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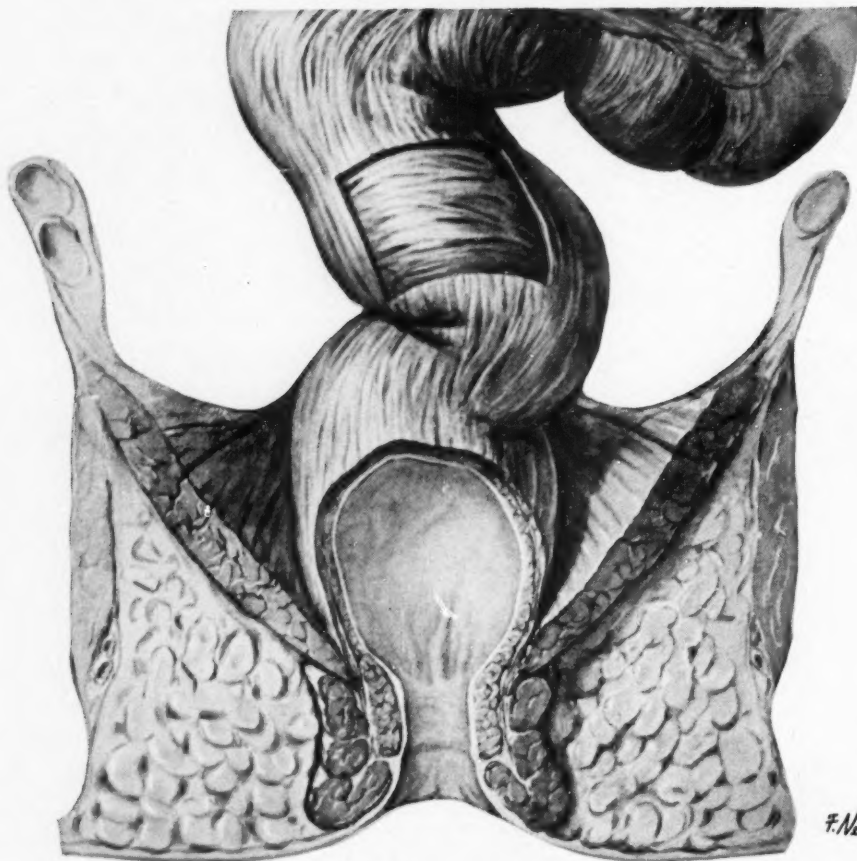
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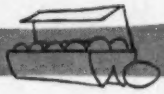







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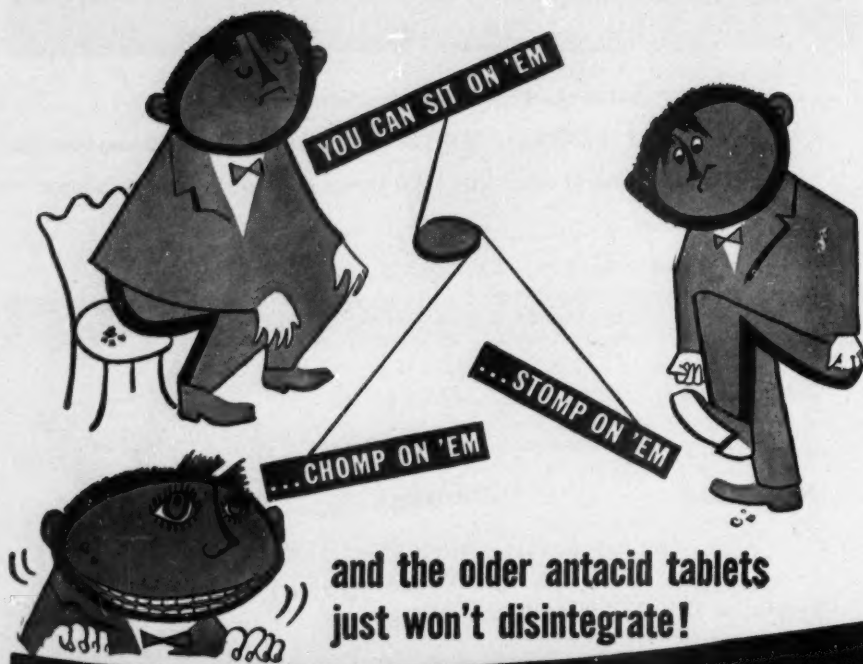
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RETROGRADE INTUSSUSCEPTION AT THE GASTROJEJUNAL STOMA: TWO CASES AND A BIBLIOGRAPHY

EDDY D. PALMER, LT. COL., M. C.,*

THE PERSON who has had an artificial stoma made in his stomach, either by a simple gastrojejunostomy or following subtotal gastrectomy, becomes vulnerable to several regional postoperative diseases. Anastomotic ulcer, functional and organic stomal obstruction, the sequels of unphysiologic gastric emptying, and postoperative gastritis are well-known. Retrograde intussusception of the jejunum into the stomach and trans-stomal prolapse of the gastric mucosa into the jejunum are rarer and are not well understood.

It is the purpose of this paper to present two case histories and a very brief discussion of retrograde intussusception of the postoperative stomach. There has already been ample discussion of this rare complication, and it is believed that presentation of a fairly complete bibliography will serve a more useful purpose at this time than would another review of part of the literature.

CASE 1

This 48-year-old veterinarian had a subtotal gastrectomy for a large gastric ulcer, which proved to be benign. The postoperative course was marked by obstruc-

*From the Gastroenterology Service, Walter Reed Army Hospital, Washington, D. C.



Fig. 1. (Case 1): The lower portion of the gastric stump contains a segment of jejunum which has undergone intussusception through the stoma. There is, however, little interference with gastric emptying.

tion at the stoma, which opened spontaneously only after 18 days. From this time on, he was able to perform full military duty, but he never felt well again. His weight stabilized 40 pounds below his normal, there was persistent foul diarrhea, and flatulence was bothersome night and day. Pancreatic supplementation plus papain helped to a moderate degree. Ulcer pain became worse postoperatively than it had been before, and after 12 months a jejunal ulcer was demonstrated. Thirteen months after gastrectomy a vagotomy was done.

Beginning three weeks after vagotomy and continuing for a year, the patient had a series of seven acute episodes of severe epigastric pain. These were frightening experiences. The first three required hospitalization, but, as they became better understood, it was possible to handle them at home. They were characterized by sudden onset of severe prostrating epigastric pain, faintness, vomiting and great nervousness. They lasted from two to 33 hours. Each episode ended suddenly and apparently spontaneously, with complete relief except for marked residual fatigue. There was no hematemesis.

During the third episode upper gastrointestinal fluoroscopy was carried out, and it was found that the distal half of the gastric stump was filled with jejunum (Fig. 1). There was little actual obstruction to the flow of barium. The jejunal segment seemed



Fig. 2. (Case 2): Intussusception of long loop of jejunum. Striated jejunal pattern can be seen at the cardia.

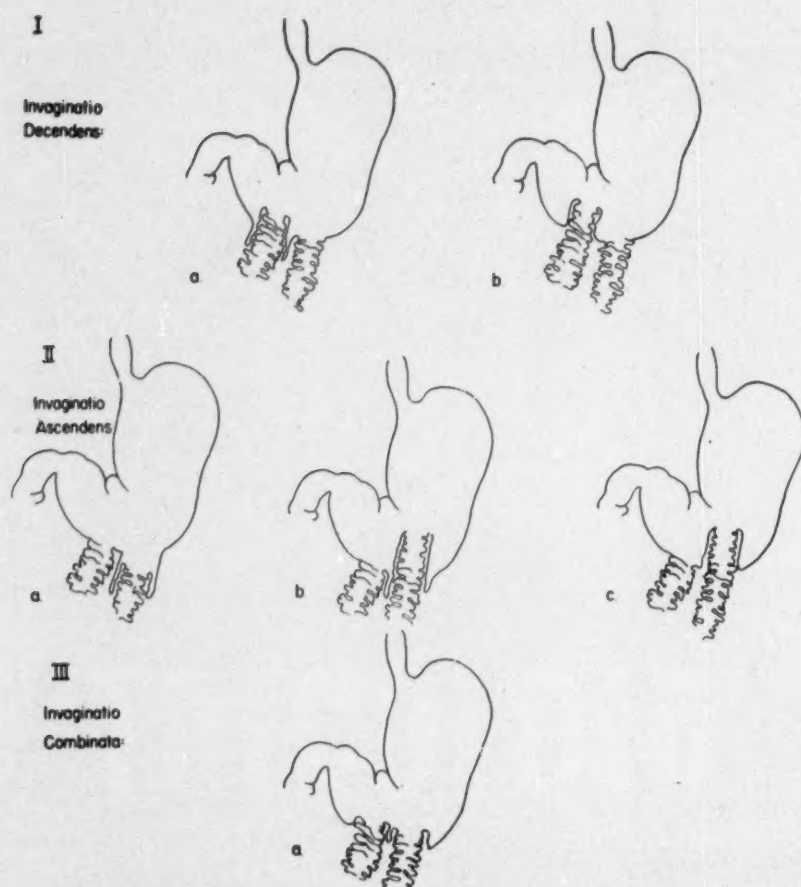


Fig. 3: Simple gastrojejunostomy: Diagrammatic representation of the various possible mechanical forms of retrograde intussusception. The terminology used here is that which appears frequently in the literature on the subject, although it is admitted that its specificity lacks practical realism.

rather mobile within the stomach, but it could not be pushed back through the stoma.

During the 12-month period of intermittent attacks several ineffective prophylactic regimens were tried. The patient was then placed on regular doses of urecholine. There have been no further acute episodes during the succeeding 14 months of observation, although undernutrition, diarrhea and flatulence persist.

CASE 2

A 32-year-old white soldier had a subtotal gastrectomy because of a duodenal ulcer which had perforated twice. Five weeks later he awoke one morning with severe nausea and epigastric cramps. He retched many times but was not able to vomit. Examination showed apprehension and tachycardia, but there was no shock and abdominal examination was normal except for marked diffuse upper abdominal tenderness. After an hour, he felt better. He drank some milk but immediately vomited and the cramps returned. Meanwhile the temperature, white blood count and scout film of the abdomen had been found to be normal. Neither free air nor obstruction could be demonstrated.

A Levin tube was passed and gavage instituted, but the gastric stump seemed to be empty. Lipiodol was injected through the tube and an hour later fluoroscopy showed that it had passed into the small bowel. The tube was then withdrawn and upper gastrointestinal fluoroscopy carried out with barium. It was found that the gastric stump was filled with jejunum and that striated jejunal mucosal pattern could be recognized as high as the cardia (Fig. 2). Nevertheless, the barium suspension began to leave the stomach within 10 minutes and only traces remained after three hours.

The patient was treated merely with sedation and bed rest. There were no systemic manifestations other than the tachycardia. Spontaneous reduction of the intussusception occurred at some time during the first night. The next morning, 24 hours after onset, the patient felt entirely well again. A second fluoroscopic examination with barium revealed a normal gastric stump, stoma, and jejunum, and the function of the organs appeared excellent.

The patient has been observed at intervals for seven months. There has been no further acute episode, and

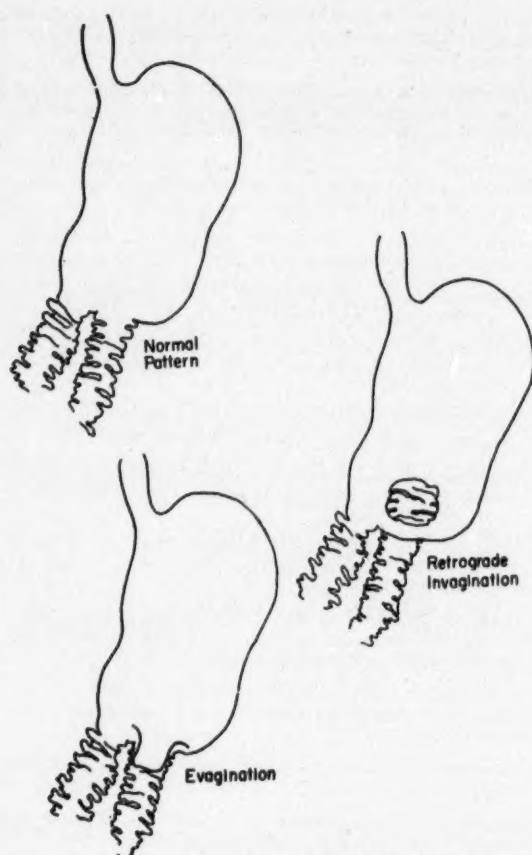


Fig. 4: Subtotal gastrectomy and gastrojejunostomy: diagrammatic representation of intussusception and of mucosal prolapse.

his subsequent postoperative course has seemed satisfactory.

COMMENT

Whenever an artificial exit is made in the stomach, rather profound physiologic alterations must necessarily follow. If the surgical procedure has induced transection of the stomach, there will have been a complete vagotomy distal to this level. This results in some minor alterations in small bowel motility, but functionally the bowel seems to suffer little. The new stoma, on the other hand, constitutes a most unphysiologic mechanism. Whether made in the intact or the partially resected stomach, the stoma creates both chemical and mechanical problems. Considering only the latter, the main local derangements are trans-stomal progression and regression of whole segments or layers of the organs on either side of the suture line (Figs. 3, 4). Such intussusceptions and prolapses are rare but may assume tremendous importance in some patients.

Probably about 125 cases of jejuno gastric intussusception have been reported. Aleman's (2) figure in 1948 was 70, and he was able to determine the anatomic derangement from the reports of 58. He classi-

fied the types into the three accepted categories: Invaginatio descendens (6 cases), Invaginatio ascendens (43 cases), and Invaginatio combinata (9 cases). The combined type occurred only a few days after operation in 6 of the 9 instances. The other types have more frequently made their presence known after months or years have passed. It has been almost exclusively the ascending type which has been found in the several fatal cases reported.

Jejunogastric intussusception is a disease of abnormal motility and functional migrations. One may speculate about the effects of segmental spasm, antiperistalsis, and postoperative relative atony, but it will be difficult to prove the usual cause. Aleman (2) stated that in no instance had any anatomic-pathologic change been found in the intussusceptum to account for invagination. One should note, however, that in 1921 Amberger (3) found at operation a jejunal fibroma just distal to a jejunal intussusception which, at the time of operation, did not involve the stoma itself.

Although the mechanism is probably the same in either instance, intussusception may occur in two distinct clinical forms, the acute obstructive and the chronic recurrent. The former presents the picture of a catastrophic high obstructive episode, with intermittent severe cramping pain and vomiting. At first there is no systemic illness, the findings being well localized over the stomach as distention, tenderness, and in some cases a palpable tumor. After a brief period hematemesis may appear. The degree of hemorrhage may be very severe, as in Moroney's (47) case. Outspoken shock may follow rapidly. Without quick diagnosis and surgical reduction, death due to obstruction, to hemorrhage, or to gangrene may ensue.

Chronic recurring intussusception does not manifest itself by any characteristic clinical picture. Although debility may be severe, the prognosis is very much better. There is intermittent partial obstruction and there may be brief periods of complete obstruction. Vomiting and epigastric discomfort are the usual complaints. The patient's stomach feels better when empty than when full. Hematemesis of important degree has rarely been reported.

The roentgenologic picture of retrograde intussusception is not difficult to understand. Both loops may have migrated trans-stomally. The filling defect within the stomach is characterized by persistence of at least a short segment of recognizable small bowel pattern. A striated appearance is produced by jejunal segments which would ordinarily lie a few centimeters from the stoma, and a more whirled pattern indicates jejunum close to the stomal region. The size of the defect gives some indication of the degree of intussusception, of course, but the parts may move almost constantly in relation to each other. The process may recur intermittently for only brief intervals at a time, so that a roentgen diagnosis may depend on fortuitous timing of the examination. On the other hand, an obviously valid roentgen diagnosis has been made in several instances, only to be followed by laparotomy at which all organs were in their normal postoperative relationships. It has been said (2) that in about 85 percent of instances of intussusception there will be enough small bowel in the stomach to produce the

typical striated effect. In other cases the roentgenologist will be able to do no more than diagnose stomal obstruction.

Gastroscopy should be particularly useful for both diagnosis and evaluation of secondary changes in the intussusceptum. In the patient reported by Coates (17) gastroscopy showed jejunum bulging through the stoma into the stomach. Gastroscopic examination in Richardson's (57) patient revealed everted jejunum in the gastric lumen, without apparent secondary mucosal changes. Wisoff (76) observed "mushroom-like" jejunal mucosa. In none of these cases were details given.

In this clinic a rather large amount of gastroscopic information has been collected on the postoperative stomach. There has not been the opportunity to study intussusception. It has been observed, however, that retrograde pouching of jejunal mucosa through the stoma is a very common finding, particularly in those stomachs which demonstrate rhythmic activity at the stoma.

SUMMARY

Two cases of retrograde jejuno-gastric intussusception following subtotal gastrectomy have been reported. Neither required surgical reduction. Urecholine appeared to help prevent recurrence in one patient. Certain aspects of this postoperative complication are briefly discussed, and a rather complete bibliography appended.

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ACUTE HEPATITIS: TOXIC OR VIRAL?

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THE HIGH incidence of viral hepatitis, both the infectious hepatitis (I. H.) and the homologous serum type (H. S.), in service personnel during World War II led to extensive studies on the epidemiology, pathology, course and treatment of this condition (1). Data were gathered which were later confirmed by studies on volunteers in whom infectious hepatitis was produced at will (2). These studies also pointed to the fact that the clinical picture of the so called catarrhal jaundice seemed to have been identical in most instances with viral hepatitis. The etiology of catarrhal jaundice appeared solved when the indication for a virus as offender was presented and appeared confirmed with the identification of the virus by Stokes and his co-workers (3).

While there is no doubt that most cases falling into the picture of catarrhal jaundice are of viral etiology there are some cases in which the viral etiology is questionable. This fact is important since thus far the identification of the virus is possible only in selected cases and since some cases of hepatitis, particularly if occurring in the civilian population may have an etiology other than viral, e.g., toxic.

To investigate this possibility the morphologic changes in the liver of proven cases of viral hepatitis (army material) were compared with the morphologic changes in the liver found in many civilian cases of primary hepatitis in a large charity hospital. From these studies morphologic criteria became available to differentiate cases of the viral type of hepatic necrosis from other cases of hepatic necrosis to which the term toxic was applied. Having established the two groups (toxic and viral) on a morphological basis, the results of their clinical and laboratory examinations were then compared and analyzed (4).

In this paper the clinical and laboratory findings of patients suffering from either type of acute hepatitis are presented and their significance in the differential diagnosis of acute hepatitis (viral or toxic) discussed.

MATERIAL AND METHOD

Almost all cases of acute hepatitis which were studied in this hospital for the past 10 years were divided into those of toxic and viral hepatitis respectively. The separation was made in most instances on the basis of morphologic changes in the liver seen in specimens obtained by punch biopsy, surgery, or necropsy. In some it was made on the basis of a specific etiology factor (viral or toxic). The laboratory findings and other clinical characteristics in the history and physical examination of these two groups of cases were tabulated and the similarities and dissimilarities compared.

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Altogether 159 cases of hepatitis with various degrees of jaundice were intensively studied during this period.

HISTORY

In the history receipt of transfusions or injections of blood, plasma, serum, or other blood products within the last 2-6 months was considered as a specific etiologic factor for viral hepatitis. Other therapeutic inoculations or needle punctures for other reasons as in drug addiction were also thought to be significant factors as was also close contact with other jaundiced (hepatitis) patients.

A history of an occupational exposure to hepatotoxic agents (chemicals, drugs, gases, fumes), or treatment with certain hepatotoxic drugs, or excessive intake of alcohol and/or poor nutrition was considered pointing to toxic hepatitis.

In the civilian population toxic hepatitis is not an uncommon clinical entity. Chances to acquire a toxic hepatitis are common in industry, in the home, and in the therapeutic field. Many hepatotoxic substances are now being used in industry, and despite all possible precautions some workers develop jaundice with toxic hepatitis. The most common offenders in this group may be listed under the following headings:

Drugs—Sulfonamides, cinchophen, arsenicals, bismuth and lead preparations, mercurials, anticonvulsants, alcohol, barbiturates, some antibiotics and endocrine substances.

Poisons—Ether, chloroform, phosphorus, carbon tetrachloride, benzene, trinitrotoluene, various other industrial solvents, insecticides and exterminating substances.

In addition to the above specific substances, toxic hepatitis (as noted by liver biopsy) may also occur in association with bacterial and parasitic infections, abnormal metabolic and degenerative processes in the body.

PHYSICAL EXAMINATION

In the physical examination particular attention was given to the general appearance and behavior of the patient (i.e. his mental state), to the presence of fever, chills, sweats, and tachycardia, to the degree and tint of the icterus, and to the appearance of the sclerae and conjunctivae. The size, consistency, and feel of the liver and spleen and the presence of adenopathy were carefully determined. Search was also made for the presence of cardiopulmonary disorders or signs of chronic disease of the gastrointestinal tract, for the presence of edema, ecchymoses, perleche, spider nevi, palmar erythema, pectoral alopecia, gynecomastia, ascites, atopic dermatitis, and hypogonadism.

LABORATORY EXAMINATIONS

In addition to the routine laboratory procedures, the following determinations of hepatic tests were done one or more times according to methods described in a previous paper (5):

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| | |
|----------------------|--|
| Sedimentation rate | Thymol turbidity |
| Serum total protein | Total serum bilirubin |
| Serum albumin | Indirect bilirubin |
| Serum globulin | Prompt direct (1 minute) |
| Serum N. P. N. | bilirubin |
| Alkaline phosphatase | Prothrombin time before |
| Total cholesterol | treatment |
| Cholesterol esters | Cephalin cholesterol flocculation test |
| Urine bile pigments | |
| Urine urobilinogen | Stool urobilinogen |

Gamma globulin turbidity

Furthermore in 122 cases one or repeated liver biopsies were performed and the specimens were studied histologically in sections stained by various methods. In 14 cases the liver was studied after the necropsy and 2 cases had both punch biopsy and necropsy.

Fifty patients were followed up to seven years and whenever practicable hepatic tests were repeated. Sixteen patients were readmitted to the hospital for various medical reasons, and in these further liver studies were done. Five female patients were admitted during this time to the obstetrical wards of the hospital and they too had repeated liver function tests.

PATHOLOGY

The biopsy or necropsy diagnosis of either type of hepatitis was made on the basis of the following criteria:

Viral Hepatitis: In early cases, patchy, diffuse, centrally accentuated liver cell damage is noted, the degree varying with the intensity of the disease. There is almost complete absence of fatty changes. There is marked proliferation of the Kupffer cells and infiltration by round cellular elements in the lobule and portal triads. Segmented neutrophilic leucocytes are hardly found. Regeneration of the liver cells is frequent, especially in the periphery of the lobules. Cells with diffusely eosinophilic cytoplasmic bodies and with pyknotic nuclei but sometimes without nuclei are found usually separated from the liver cell plates. They simulate Councilman bodies.

In older cases, liver cell damage may be completely absent and Kupffer-cell mobilization with dense histiocytic infiltration of the portal triads is present where a number of lipofuscin pigments are seen.

Toxic Hepatitis: Here the liver cell damage is zonal and is indicated by various stages of coagulation necrosis. Fatty metamorphosis is usually slight. The periportal triads may be free of cellular infiltration but in the sinusoids some histiocytic elements and dense infiltration with segmented leukocytes are found. The liver damage in general is out of proportion to the bile stasis and severe liver damage with little bile stasis may be seen. Necrosis of the liver cells in the center of the lobules differentiates this form of fatty metamorphosis from simple fatty liver.

CLINICAL OBSERVATIONS

Etiologic Factors

Sex, Race and Age: Of the 159 patients studied, 54 were classified as belonging to the toxic and 105 to the viral group. In the toxic group, there were 35 males and 19 females; in the viral group, 48 males and 57 females. In the former (toxic) group there were 24 whites and 30 colored while in the latter (viral) there were 27 white, 77 colored and 1 other, respectively. The ages of these patients ranged from the second to the eighth decade in both types, although the younger age groups predominated in the viral form (Table 1). The youngest patients were 19 in the toxic and 16 in the viral type, the oldest 75 and 82 years, respectively.

Precipitating and Predisposing Factors: In the toxic group a significant number of patients had a history of exposure to one of the many hepatotoxic substances either from ingestion (drugs, etc.) or from occupational hazards—by inhalation or skin absorption. Cinchophen, arsenic, and barbiturates were the most commonly ingested drugs while the trinitrotoluenes, benzenes, etc. were the most commonly encountered ones among the occupational hazards. Alcohol was a predisposing factor in a moderate number of cases. Pneumococcal and other bacterial infectious processes were the probable causative factors in others.

In the viral group, 47 had histories of having received transfusions of blood or blood products within the past six to eight months. "Homologous serum hepatitis" proved to be common also in drug addicts (6), so that an increasing number of young heroin addicts are being admitted with this disease. In confirmation with other reports (7) we also observed instances of viral hepatitis following tattooing, the use of mumps convalescent serum and of topical thrombin, and also among workers in blood banks, in plants dealing with processing of plasma or other blood products, and in clinical laboratories. In one patient serum hepatitis occurred following the injection of influenza vaccine.

TABLE I
DIFFERENCES IN PERCENTAGE INCIDENCE OF AGE GROUPS, SEX
AND RACE IN THE TWO FORMS OF HEPATITIS

| Disease | Age Group | | | | | | | Sex | | Race | | |
|-------------------|-----------|-------|-------|-------|-------|-------|-----|------|--------|-------|-------|--------|
| | -20 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70+ | Male | Female | White | Color | Others |
| Infect. Hepatitis | 11.4 | 52.4 | 12.4 | 10.5 | 5.7 | 3.8 | 3.8 | 45.7 | 54.3 | 25.7 | 73.3 | 1.0 |
| Toxic Hepatitis | 1.8 | 20.4 | 29.6 | 20.4 | 13.0 | 9.3 | 5.6 | 64.8 | 35.2 | 44.4 | 55.6 | 0 |

SYMPTOMATOLOGY

While most patients with acute hepatitis had, on admission to the hospital, certain specific complaints and findings in common, some of these symptoms seemed to be more pronounced in one form than the other. A careful analysis of the presenting complaints and findings in these cases of acute hepatitis revealed certain differences in the severity and in the incidence of some symptoms and signs which help differentiate the two groups of hepatitis.

Toxic Hepatitis—Subjective Findings: The toxic form was often ushered in by fever, chills, and headaches, as would be expected from the occasional underlying basis, e.g. pneumonia or other infections. The patients complained of various degrees of abdominal pain, nausea, vomiting, anorexia and distention. Some complained of associated symptoms referable to the chest or heart or kidneys. Diarrhea was also not infrequent. Many complaints were secondary to the toxic substances responsible for the disease and overshadowed the hepatic symptoms. The symptoms may persist for days after admission.

Infectious Hepatitis—Subjective Findings: In the prodromal stage, these patients presented mainly an influenza-like picture as manifested by feverishness, chilliness, anorexia, nausea, occasionally vomiting, malaise, headache, fatigability, muscular aches, flatulence, and soft stools. A marked distaste of food and cigarettes was present in some (8); in others, urticaria, herpes labialis and arthralgia was present. Occasionally, epigastric or upper abdominal distress (severe enough, at times, to simulate as acute abdomen) was prominent while in some chills and temperatures of 103-104 were found. Jaundice was often very slight and the color of the excreta (urine and feces) had not changed perceptively enough to the lay observer.

In the icteric state, the patients complained more of the jaundice and changes in the color of urine and feces. They also complained of gastrointestinal symptoms—anorexia, nausea, and vomiting, and were list-

less and fatigued. Anorexia persisted in some even after the nausea and vomiting had disappeared.

Some patients, however, were almost symptom-free and entered the hospital merely because of the yellow discoloration in their eyes and skin.

Toxic Hepatitis—Objective Findings: These patients were usually older and appeared as a rule, much sicker than those with the infectious type. They seemed "toxic," hypohydrated, apathetic or lethargic and some occasionally delirious. Bradycardia was rare; there was usually a rapid pulse rate associated with fever over 101 (Table 2). Signs of associated or causative disease in the pulmonary or cardiorenal systems were occasionally present. The icterus was fairly severe and usually of reddish tint, if the patient was seen early. The liver was usually enlarged, smooth and moderately tender to pressure. Edema and ascites were common. Cervical adenopathy and splenomegaly were rare. Toxic dermatitis was occasionally seen.

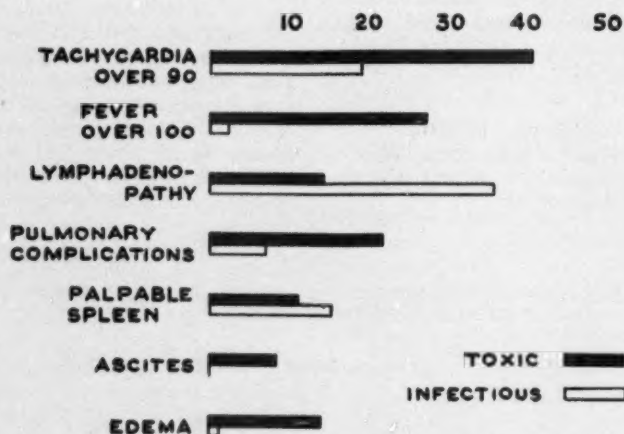
Viral Hepatitis—Objective Findings: Patients with viral hepatitis were usually younger. Many of them did not appear very ill and seemed to have entered the hospital chiefly because of the jaundice. Rarely, they appeared very ill, mentally disturbed or comatose.

These patients exhibited all degrees of icterus, with a reddish to greenish tint depending on the amount of intrahepatic obstruction, but more commonly showed severe icterus than the toxic group. In some mild pruritus was present initially. Fever of over 101 and pulse of over 90 were comparatively rare (Table 2). Signs of upper respiratory infection were present in the acute form; in some of them injection of the scleral conjunctiva was noted.

Cervical adenopathy was frequently noted, especially in the posterior chain, and at times, the glands were enlarged to a degree suggestive of infectious mononucleosis. This adenopathy was more common in infectious hepatitis than in serum hepatitis.

The liver varied in size, but it was usually tender

TAB.2. PHYSICAL FINDINGS



Percentage incidence of abnormal clinical findings in the two types of hepatitis.

on palpation and especially on percussion. Characteristically, a dull ache persisted in the liver region for some hours after percussion. Pressure on the liver in the right costo-vertebral angle elicited tenderness in some. The spleen was commonly enlarged but usually was not tender. Ascites and edema were rare, while associated signs of cardiac and pulmonary disease were extremely rare. (Table 2).

LABORATORY RESULTS

While most of the patients with acute hepatitis had abnormal hepatic tests, certain tests were more frequently abnormal in one group than in the other and certain combinations of tests occurred more commonly in one of the two groups. It should be noted that only the results of the initial tests were used in the diagnostic evaluation of these cases.

Toxic Hepatitis:

In these patients the hemoglobin was usually below 50 per cent, the white blood count over 10,000, and the polymorphonuclear leucocytes over 85 per cent; macrocytosis and lymphocytosis were not common. The urine contained 3 plus to 4 plus albumin and 4 plus urobilinogen in a moderate number of cases. Four plus bilirubinuria occurred in about half of the cases, the remainder having smaller amounts of bilirubin in the urine (Table 3).

The flocculation and turbidity tests were less commonly strongly positive in this group. Thus, only 46 per cent of the cases had a 3 plus or 4 plus flocculation as against 54 per cent which had 0 to 2 plus flocculation. Similarly 33.3 per cent had a thymol turbidity of less than 5 units and 33.3 per cent had one of over 10 units. Total protein values were, as a rule, lower in this group, as also were the albumin values. The

alkaline phosphatase was less than 5 Bodansky Units in 27 per cent of the cases. The cholesterol esters were markedly decreased in this group with 36 per cent of the cases having values of less than 50 per cent and 7 per cent of them having less than 25 per cent esters. Another striking fact was the incidence of high nonprotein nitrogen values in this group. Fourteen per cent had N.P.N. values of 60-100 and 14 per cent of over 100 mg. per cent.

Viral Hepatitis:

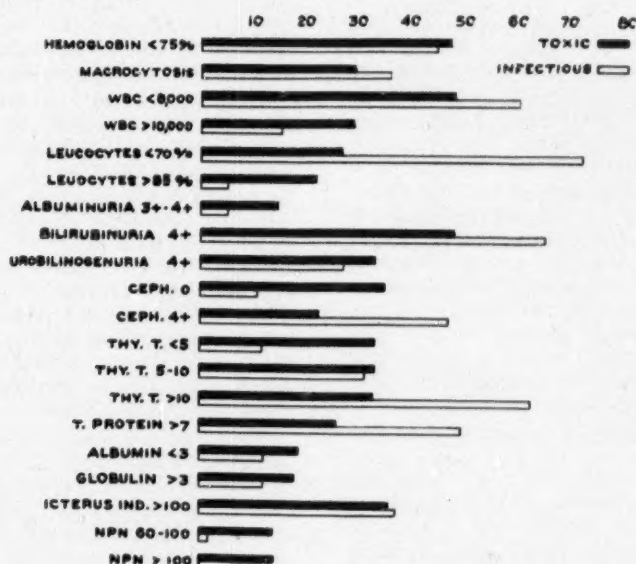
These patients had, as a rule, higher values for the red blood count and hemoglobin, and lower values for the white blood count and polymorphonuclear leucocytes. More than half of them had a white blood count below 8,000 (12 per cent below 5,000) and polymorphs below 70 per cent (11 per cent below 50 per cent). The lymphocytes and monocytes were usually increased, the blood smear occasionally simulating that of infectious mononucleosis. Macrocytosis was common. Thus, the blood picture commonly seen in cases of viral hepatitis was that of leucopenia with lymphocytosis and monocytosis and a slight macrocytic, hypochromic anemia.

While marked bilirubinuria and urobilinogenuria were frequent, a 3 plus or 4 plus albuminuria was very rare (4.3 per cent).

The flocculation and turbidity tests were strongly positive with 75.4 per cent having 3 to 4 plus cephalin flocculation tests. Sixty-two per cent of the patients had a thymol turbidity above 10 with values up to 30. Only a small number had an albumin below 3 grams per cent. High values for the icterus index were somewhat more common in this group as also high values for the alkaline phosphatase. Only about

TABLE 3.

LABORATORY WORK



Percentage incidence of abnormal laboratory results in the two types of hepatitis.

one-third of the cases had cholesterol ester values of less than 50 per cent and hardly any a nonprotein nitrogen of over 60 milligrams per cent (Table 3).

TEST GROUPINGS

In addition to the above differences in the results of individual hepatic tests, certain groups of tests appeared to be more characteristic of one than of the other type of hepatitis. Thus, a high bilirubin was commonly associated with a high thymol turbidity in the viral group, but with a moderately elevated thymol in the toxic group. Similarly, a high sedimentation rate was usually accompanied by a high thymol turbidity in the viral group, and by a moderate elevation in the toxic group. Finally, a 3 or 4 plus cephalin was generally present in the toxic group only with marked icterus, while in the viral form, it sometimes occurred with moderate icterus.

CLINICAL COURSE

Toxic Hepatitis:

These patients, while quite ill and, at times, delirious during the height of the disease, usually improved moderately rapidly once the acute stage was over. The gastro-intestinal symptoms disappeared, appetite returned and the general condition improved. The icterus cleared fairly rapidly at times, seemingly from day to day the liver decreased in size and the patients were soon anxious to leave the hospital.

Some patients, however, particularly those with a severe associated disease, remained desperately sick for a long time before recovery or death ensued. Even when comatose, some recovered with successful treatment of the underlying toxic factor, in contrast to patients with viral hepatitis who succumbed within a few days once cerebral symptoms had appeared. Clinical improvement seemed to become apparent before striking changes were noted either in the hepatic function tests or in the morphologic appearance of hepatic biopsy.

Viral Hepatitis:

These patients generally had a somewhat less stormy but more prolonged course than those with toxic hepatitis. Those who entered following a mild upper respiratory prodromal syndrome had few symptoms and improved rapidly, as did their liver function tests. Those who had had marked prodromal symptoms continued to have anorexia, nausea, bloating and upper abdominal distress for some time (7-10 days), and only slowly regained their appetite and general feeling of well being. In some, mild symptoms of aching in the right upper quadrant especially on slight exertion, some anorexia, food selectivity, distaste for fatty foods with associated fat intolerance, feeling of fatigue, and vasomotor disturbances persisted throughout the hospital stay, even after disappearance of jaundice.

Patients who continued with symptoms of liver dysfunction long after the acute stage had passed gradually went into a stage of chronic hepatitis. They continued to exhibit symptoms and signs of the preceding hepatitis although to a lesser degree.

Another group apparently recovered completely from the original hepatitis, but complained of recurring symptoms after varying intervals. These recur-

rences seemed to be brought on by such factors as physical overactivity, excess of food or drink, exposure to hepatotoxins, inclement weather or intercurrent infection. The frequency and severity of these recurrences depended upon the inciting factors. In some of the female patients, pregnancy and the puerperium caused recurrence of certain symptoms. Occasionally, no apparent inciting factor was present.

PROGNOSIS

The two types of hepatitis also differ from the prognostic point of view. The toxic group had a mortality of 24.1 per cent, while of the 14 patients followed up, only two complained of weakness. One of these was later readmitted as a possible gall bladder disease. One patient was later readmitted as a bronchopneumonia and expired.

In the viral group the mortality was 7.6 per cent while "liver" symptoms (anorexia, weakness, dull right upper quadrant ache, fatigue, etc.) persisted in over 50 per cent of those who attended the gastro-intestinal clinic. Two patients had to be readmitted to the hospital because of these symptoms but recovered again and left the hospital.

DISCUSSION

Clearly, the most important differential diagnosis in the icteric patient is between jaundice due to primary hepatitis from that due to extra-hepatic obstruction. However, at times it is also important to decide whether the hepatitis is toxic or viral in origin inasmuch as differentiation between the two types is frequently of practical therapeutic importance. The clinician should recognize the two types of primary hepatitis and be aware of the fact that labeling every jaundice case not due to an extra-hepatic obstruction as viral hepatitis is occasionally as objectionable as the previous nomenclature of catarrhal jaundice. While patients with a definite history of carbon tetrachloride or chloroform poisoning will often be correctly diagnosed as toxic hepatitis, it is emphasized that there are other cases of toxic hepatitis in whom the etiologic toxic factor must be carefully and often tediously elicited.

Toxic hepatitis differs from the viral type regarding incidence (9) (seasonal, localities, epidemics), frequency and predominance in certain groups (racial, sexual and age). The subjective symptoms, physical findings, laboratory results, findings on liver biopsy or necropsy specimens, clinical course and outcome are different in toxic hepatitis. These differences are, at times, poorly demarcated and a differential diagnosis can be made only later in the course of the disease. Thus, for example, the jaundice developing during arsenical therapy may be either toxic or viral in origin and the differentiation may only be made after an interval when certain symptoms and findings have become more predominant.

As a rule toxic hepatitis is a priori a more serious condition. Most of the patients suffering from toxic hepatitis enter the hospital in a precarious state. At times they are even too ill to give a reliable history on admission. They also show more vividly the results of their complaints—nausea, vomiting, anorexia, diarrhea, fever, etc.—since they appear hypohydrated, lethargic, feverish and at times delirious. Their pulse

is usually rapid and the temperature high, particularly in those in whom the toxic hepatitis is secondary to some pulmonary disease.

While hepatic enlargement is common in hepatitis the largest livers were found in cases of toxic hepatitis. In patients with toxic hepatitis who had an alcoholic background the livers were at times tremendously enlarged, reaching almost to the iliac crest. Very large livers were also noted in two cases of cinchophen ingestion, in one case of carbontetrachloride poisoning and in one case of chronic pancreatitis with acute exacerbation. The large livers of the toxic hepatitis cases appear also more tender to simple palpation than those of patients with infectious hepatitis. This tenderness may at times be severe enough to suggest, in conjunction with the abdominal pain, the likelihood of an acute surgical abdomen, so that surgical consultation was requested in several instances. The hepatomegaly noted in our cases of toxic hepatitis did not decrease when the patients' condition became progressively worse so that at post mortem some livers weighed up to 3000 grams or more in contrast to the small livers, 700-1200 grams of the fatal cases of infectious hepatitis.

The laboratory examinations in toxic hepatitis show pathologic results particularly in those tests which more or less are related to changes in the hepatic parenchymal cells rather than in the mesenchymal (R.E.S.) tissues. Thus the cholesterol esters and albumin are on the average lower in toxic than in viral hepatitis. However, the total globulin including gamma globulin are higher and the flocculation and turbidity tests relating to the gamma globulin are more frequently positive in the viral type of hepatitis. The cephalin flocculation was more often negative and the thymol turbidity low particularly in the toxic hepatitides due to alcoholic debauché. Similarly the association of toxic hepatitis with leucocytosis and high or normal polymorphonuclear leucocyte count was quite striking in comparison with the relative leucopenia and lymphocytosis of the viral type.

That toxic hepatitis is a more serious illness than the viral type may be gleaned from the mortality in these two types, which was 24.1 per cent in the former and 7.6 per cent in the latter one. While in the civilian population of a charity institution representing all ages and all degrees of physical fitness, the mortality of any disease will be higher than in the young patients of the armed services, the differences are nevertheless significant despite the fact that the mortality of 7.6 per cent in our cases of viral hepatitis was much higher than the usually quoted figure of 0.2 - 0.7 per cent. We believe that our 7.6 per cent mortality in viral hepatitis is due to the mortality in patients with homologous serum jaundice which is much higher in a private hospital than in the services because of the nature of the primary condition necessitating blood transfusion.

While the immediate prognosis in toxic hepatitis appears to be more serious than in viral hepatitis the final outlook seems better except perhaps in the alcoholic group. Patients with toxic hepatitis usually improve more rapidly once the convalescence stage sets in and are usually free of symptoms later on. Cases of viral hepatitis, on the other hand, require longer con-

valescence and are more prone to residual symptoms. Of our cases with toxic hepatitis only a small percentage progressed into the chronic stage. The incidence of chronic hepatitis in the viral type was much higher but this was probably also attributable to the nature of the clinical material—malnourished patients from poor hygienic surroundings, alcoholics, narcotic addicts and older individuals with associated diseases. That viral hepatitis may be more serious in older patients and in those with associated diseases has been accepted by other workers in this field (10).

The insidious nature of viral hepatitis makes prognosis more uncertain than in toxic hepatitis. The dictum "each hepatitis case a potential case of acute yellow atrophy" has been in our experience more applicable to viral than to toxic hepatitis: some patients may appear comparatively well one day, only to become stuporous within 24-48 hours and die within another 48 hours. On the other hand, cases of toxic hepatitis which proceed to hepatic coma and death, usually run a progressively downhill course.

The need for differential diagnosis between the toxic and viral form must be considered also from the therapeutic point of view. While much of the pathologic physiology of viral hepatitis is unknown, present knowledge points to an active process proceeding rapidly to necrosis, disappearance of the liver cells, and, occasionally, collapse of entire lobules (11). In toxic hepatitis, on the other hand, there appears to be a gradual breakdown of the hepatic cells with fatty infiltration and degeneration before necrosis; moreover, the associated or responsible primary disease may affect the hepatic pathology. Hence, in toxic hepatitis, specific therapy is often applicable, while in viral hepatitis, except for the prophylactic use of gamma globulin (12), the treatment is usually only supportive. The specific therapeutic procedures in toxic hepatitis include the use of substances related to enzyme activity (e.g. Bal in hepatitis due to heavy metals), to lipid transport (e.g. methionine and choline in hepatitis associated with fatty liver (13), and for combatting various pyogenic and other infections.

While the advent of the wider spectrum antibiotics—*aureomycin* (14) and *terramycin*—and of *ACTH* and *cortisone* (15) has somewhat modified the treatment of both types of hepatitis, their best results are still noted in cases of toxic hepatitis.

SUMMARY

Primary hepatitis exists in two forms. These two forms of hepatitis—viral and toxic—present certain differences in their etiology, symptomatology, and laboratory tests.

The clinical course and prognosis vary markedly in these two types of hepatitis. Specific therapeutic procedures are usually present for cases with the toxic type but absent for those with the infectious type.

Differentiation between the two types of primary hepatitis is more than just of academic interest, and hence, it should be attempted in every case.

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NEWER CLINICAL AND LABORATORY STUDIES IN THE AGED

III. URINARY TEST FOR GASTRIC SECRETION OF HYDROCHLORIC ACID IN PATIENTS 80 TO 100 YEARS OF AGE

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WITH THE greater number of the population attaining and living a healthy life beyond the age of 60 and 70, it becomes essential for the profession to be cognizant of what "normal" metabolic functions take place. Since the patients admitted to this institution have diseases characteristic of this age group, it affords one an opportunity to study "normal geriatric medicine."

Our previous publications on blood lipid studies in the same patients (1, 2) have revealed low levels not related to malnutrition, avitaminosis or wasting diseases. Other authors mention the increasing frequency of permanent achlorhydria associated with age by the progressive gastritis, anemia, malnutrition and debilitation (3). Since known malignancy and active tuberculous patients are not admitted to this institution, it seemed all the more important to ascertain what percentage of geriatric patients would show anacidity and the cause thereof.

Recent favorable reports of tubeless gastric analysis (4-8) prompted us to compare this method with gastric intubation as a method of procedure for geriatric patients. The report concerns our findings in 95 male and female "normal" patients, age 80-100 years.

METHODS OF STUDY

All medications such as steroid compounds, vitamin preparations, quinine or related drugs and sedatives were omitted on the day preceding the test. No food was permitted after midnight. On arising, the patient was instructed to urinate and discard the specimen. Breakfast and liquids were omitted. A capsule containing 250 mg. of caffeine sodium benzoate was given followed by a glass of water, coffee or tea without cream, milk or sugar. Secretory stimulants such as histamine diphosphate were not used because of the advanced age of the patients. One hour later, the patient voided and the entire quantity of urine collected,

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The quininum resin used in this study was generously supplied by the Squibb Institute for Medical Research, New York, New York. It is now manufactured under the trade name of "Diagnex."

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marked as "control urine." A mixture of 2.0 grams of quininum resin was emptied into a glass of water, stirred well, and given to the patient. Urine was collected one hour and two hours after taking the resin compound. The specimens were marked "2" and "3."

The patient was told to empty the bladder completely each time. If urination ahead of a scheduled time was necessary the amount was added to that passed at the next designated time. In the last 25 patients this procedure was modified in that only a single test specimen of urine was collected two hours after the administration of the resin compound. No urine was collected after the 2 hour period.

COMPOSITION AND ACTION OF QUININIUM RESIN

Diagnex is a quininum resin indicator, which operates through a displacement of quinine by the hydrogen ions of the gastric hydrochloric acid. When free gastric acid (HCl) is present in the stomach the quinine (QH+) of the indicator compound is displaced by the hydrogen (H+) of the gastric acid. The quinine hydrochloric (QHCl) thus formed is absorbed in the small intestine. The quinine will appear in the urine within two hours after taking of the compound and produce fluorescence. When no free acid (HCl) is present in the stomach, the quinine (QH+) of the indicator compound is not displaced in the stomach. No quinine will appear in the urine specimens and fluorescence will be absent. This test indicates the presence or absence of free hydrochloric acid in the stomach. The results of the test are not quantitative.

TECHNIQUE OF ANALYSIS

Each urine specimen was diluted to 300 cc. with distilled water. A narrow-bore assay separatory funnel calibrated as to the amount of solution was used. The diluted urine was poured into the funnel up to mark I, corresponding to 30 cc. of solution. 0.5 cc. of half-normal sodium hydroxide and 15 cc. of ether were added up to mark II (45.5 cc. solution). The funnel was inverted gently five to six times. The funnel was permitted to stand for separation of the layers adding a few drops of 95% ethyl alcohol to achieve sharpness. The contents of the funnel were drained off and discarded to the top of the ether layer at mark III (8.2 cc.). 5 cc. of tenth-normal sulfuric acid were added to mark IV (13.2 cc.) shaking about ten times, allowing the layers to separate and 5 cc. of the lower layer were drained off for fluorescent examination.

METHOD OF PREPARING STANDARD SOLUTION

A stock solution of quinine sulphate is prepared by dissolving 12 mg. of quinine sulphate in 100 cc. of tenth-normal sulfuric acid in a volumetric flask. This

provides a concentration of practically 0.1 mg. of quinine per cc. The stock solution keeps indefinitely, but fresh standards for comparison must be prepared every few days. Fresh standard solutions can be made by diluting 0.3 cc. of the stock solution in the tenth-normal sulfuric acid to a volume of 15 cc. This solution, containing 2 micrograms of quinine per cc. is placed in six separate test tubes with volumes varying from 0.12 cc. to 0.75 cc. of the stock solution. Tenth-normal sulfuric acid was added to make 5 cc. in each test tube. This permitted 0.25 mcgm. to 1.5 mcgm. quinine in each standard, equivalent of 5 to 30 mcgm. of quinine in the urine.

MEASUREMENT OF FLUORESCENCE

This was estimated by the Blak-Ray Lamp, Model X-4 in a darkened room by visual comparison with standard solutions containing known amounts of quinine under ultra-violet light.

INTERPRETATION

The control sample of urine must first be determined for fluorescence. If the result shows fluorescence corresponding to 15 mcgm. or more of quinine, the test is disregarded and repeated after a week. This may be evidence that the medications as B-complex vitamins, quinine or steroid compounds were not eliminated. If the result on the urine control corresponds to 5 to 15 mcgm. of quinine, the urine samples may be examined. The amount of fluorescence seen in the control must be subtracted from each of the two test samples. If the amount of fluorescence of the urine control corresponds to less than 5 mcgm. of quinine, it can be ignored and not subtracted. The total of the 2 specimens of urine or the second hour specimen should result in 25 mcgm. of quinine or more to determine the presence of free gastric hydrochloric acid. A range of 15 to 25 mcgm. of quinine may be evidence of hyp acidity. The test is repeated after seven days or corroborated by intubation.

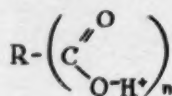
DISCUSSION

Achlorhydria is uncommon in healthy infants and children and its occurrence is noted more frequently with advancing age (9). Vanzant and associates found 14.5% of apparent achlorhydria (10) in patients with no diseases of the gastro-intestinal tract. The incidence of achlorhydria dropped slightly after the age of 60 suggesting that persons with achlorhydria are not so hardy or so long lived as those who have strongly acid gastric juice. Achlorhydria is slightly more common in the female than in the male according to some observers (11). Winkelstein (12) found the percentage of achlorhydrias among 5,585 patients was 2.2%. Pollard (13), using the histamine test, found 10.4% of achlorhydria in males and 14.1% in females. Faber (14) explains the increasing frequency of permanent achlorhydria with age by the progression of gastritis. Rafsky and Weingarten (15) found 17.0% of achlorhydria in normal patients past 65 years of age, none of whom had peptic ulcer syndrome.

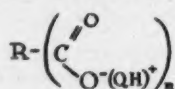
Cation exchange indicator compounds are prepared by replacing the hydrogen cations of the carboxylic acid groups present in cation ion exchange resins with cations which are not normally present in the

body. These can be replaced by hydrogen cations to determine the presence of free hydrochloric acid. Such conditions, called special indicator ions, must be non-toxic, readily absorbed from the stomach or small intestine, and easily detectable in the blood, urine, and/or saliva. Cation ion exchangers such as Amberlite-IRC-50 or Amberlite XE-96 when subjected to the action of special indicator cations in aqueous solution form a cation exchange ion indicator.

By the employment of this principle quininium exchange indicator compound has been produced:

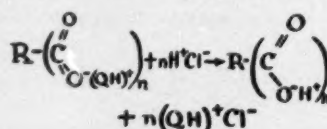


Formula No. 1: Amberlite (cation exchanger)



Formula No. 2: Diagnex (Quininium cation exchange indicator compounds IEC-QH).

When diagnex is subjected to the action of hydrogen cations of gastric hydrochloric acid the quininium cations are replaced by the hydrogen ions:



Formula No. 3

The compound contains approximately 18 mg. of available quinine per gram of resin. Doses of 2 grams are administered. The quinine hydrochloride so formed is absorbed from the small intestine and about $\frac{1}{3}$ of it is then excreted in the urine. The first two hours after the oral examination of this indicator compound are the critical hours in the excretion of the quininium cations to determine whether the quinine cations have been displaced by the hydrogen ions of free gastric hydrochloric acid or to a lesser extent by the cations present in the secretions in the small intestines.

RESULTS OF STUDY

95 male and female "normal" patients age 80 to 100 years were studied. The conditions commonly encountered were arthritis, hemiplegia, sclerosis, Parkinsonism, diabetes, etc. Many patients were here because of social and economic domestic conditions.

Total of 95 normal geriatric patients studied showed 66 (69.5%) had acidity while 29 (30.5%) had no

TABLE 1

PRESENCE AND ABSENCE OF ACIDITY BY THE TUBELESS METHOD IN "NORMAL" GERIATRIC PATIENTS

| Tubeless Method for Acidity | Total Number Patients | Percentage |
|-----------------------------|-----------------------|------------|
| positive | 66 | 69.5% |
| negative | 29 | 30.5% |

acid (Table I). The 29 patients who exhibited achlorhydria with the tubeless method were checked by gastric intubation. 27 such determinations were made. Three negative urine tests revealed three positive results for acidity with the tube method, showing a discrepancy of 11.1% and a comparative value of acidity both by gastric analysis and urinary examinations of 88.9% (Table II).

44 patients had gastro-intestinal x-ray examinations (Table III). 23 patients had a negative x-ray finding

(52.3%). 14 of these 23 patients demonstrated the presence of acid by the urinary test (60.9%). The other x-ray diagnoses were of no significance except for one case of antral gastritis with hyperchromic macrocytic anemia, one with gastric malignancy, one with duodenal ulcer, and two with gastric ulcer. Interestingly the above patients displayed acidity by the tubeless method.

The comparative value of the positive tubeless method for acidity determination (69.5%) in all 95 patients approximated that encountered with negative and varied insignificant gastro-intestinal x-ray findings (70.4%) in 44 patients (Table IV).

TABLE II

DIFFERENCE BETWEEN TUBELESS AND INTUBATION METHODS FOR ACIDITY DETERMINATIONS IN "NORMAL" GERIATRIC PATIENTS

| Tubeless Method Negative | Intubation Method Negative | Method Positive | Percentage |
|-----------------------------|-------------------------------|--------------------|------------|
| 24 | 24 | | 88.9% |
| 3 | | 3 | 11.1% |
| Total 27 | 24 | 3 | 100.0% |
| Refused 2 | | | |

CONCLUSIONS

1. Tubeless gastric acidity was studied in "normal" geriatric patients 80-100 years of age, male and female.
2. Achlorhydria was found in 30% of "normal" geriatric patients while acidity was present in 70% of the patients.
3. Gastro-intestinal x-rays showed normal studies in 52% of the patients. Only one case of gastric malignancy, two of gastric ulcer, and one of duodenal ulcer were encountered.

TABLE III

GASTRO-INTESTINAL CONDITIONS ENCOUNTERED IN "NORMAL" GERIATRIC PATIENTS BY X-RAY SERIES WITH THE PRESENCE OR ABSENCE OF GASTRIC ACIDITY BY THE URINARY METHOD

| X-ray Diagnosis | Patients X-rayed | | Tubeless Method for Acidity Determination | | Negative Urinary Acidity Tests Compared to Intubation Method | |
|-----------------------------|---------------------|---------|---|----------|---|----------|
| | Number | Percent | Positive | Negative | Positive | Negative |
| Normal | 23 | 52.3 | 14 | 9 | 1 | 8 |
| Pylorospasm | 5 | 11.3 | 5 | | | |
| Hiatus hernia | 4 | 9.0 | 3 | 1 | | 1 |
| Prolapse gastric mucosae | 4 | 9.0 | 2 | 2 | | 2 |
| Duodenal diverticulum | 2 | 4.4 | 1 | 1 | | 1 |
| Gastric ulcer | 2 | 4.4 | 2 | | | |
| Antral gastritis | 1 | 2.4 | 1 | | | |
| Cancer of stomach | 1 | 2.4 | 1 | | | |
| Duodenal ulcer | 1 | 2.4 | 1 | | | |
| Duodenitis | 1 | 2.4 | 1 | | | |
| Total | 44 | 100.0 | 31 | 13 | 1 | 12 |

TABLE IV

COMPARATIVE PERCENTAGE VALUES OF TUBELESS METHOD FOR ACIDITY DETERMINATIONS IN "NORMAL" GERIATRIC PATIENTS WITH NORMAL AND VARIED INSIGNIFICANT X-RAY FINDINGS

| Status | Number of Patients | Urinary test for gastric secretion of hydrochloric acid—percentage | |
|-------------------------------|--------------------------|---|----------|
| | | Positive | Negative |
| Total | 95 | 69.5 | 30.5 |
| Normal G.I. X-rays | 23 | 60.9 | 39.1 |
| Varied G.I. X-ray findings | 44 | 70.4 | 29.6 |

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nancy, two of gastric ulcer, and one of duodenal ulcer were encountered.

4. Positive tubeless gastric acidity values (69.5%) approximated the normal and varied insignificant gastro-intestinal x-ray findings (70.4%).

5. Discrepancy between the negative tubeless gastric acidity method and the positive gastric intubation for acidity was 11.1%.

6. The convenience and economy of the tubeless gastric acidity method makes it possible to screen large numbers of geriatric patients and eliminate unnecessary x-ray examinations.

7. The urinary test for gastric secretion of hydrochloric acid (tubeless method) should be advocated

in geriatric patients and in conditions that would contra-indicate intubation.

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A STATISTICAL COMPARISON OF THE BLOOD LYSOZYME ACTIVITY OF NORMAL ADULTS AND OF PATIENTS WITH LOCALIZED AND GENERALIZED CARCINOMATOSIS*

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THIS IS the study of blood lysozyme activity in an unselected group of 35 patients with varying stages of malignancy. It was made possible by our method of assay previously described (1). Lysozyme was selected for study because it is normally found in many body fluids and any variation might be significant either in diagnosis or pathogenesis.

RESULTS

The previously described method (1) of determining lysozyme activity in the blood was employed successfully on 35 cancer patients with localized and/or generalized carcinomatosis. The results indicated an increase in the lysozyme activity as compared to normal controls but the distribution curves in the two groups overlap too much to be of diagnostic clinical value. The normal control group, consisting of 77 individuals, was reported (1, 2) to have a mean lysozyme activity of 5.64 mcg. of lysozyme per ml. of whole blood with a standard deviation of 2.05 (36.6 per cent) and a standard error of 0.234. The carcinoma group in this series of 35 patients was found to have a mean activity

of 9.26 mcg. of lysozyme per ml. of whole blood with a standard deviation of 4.18 (45 per cent) and a standard error of 0.706. Table 1 shows the spread of both

TABLE I
NUMBER AND PER CENT OF INDIVIDUALS OF EACH GROUP FALLING INTO CERTAIN RANGES OF LYSOZYME ACTIVITY FROM WHICH THE DISTRIBUTION CURVES WERE DRAWN

| Micrograms Lysozyme Per ml. Blood | Number of Normals | Per Cent of Normals | Number of Carcinoma Patients | Per Cent of Carcinoma Patients |
|--|-------------------------|---------------------------|---------------------------------------|--------------------------------------|
| 0-2 | 3 | 3.9 | 0 | 0 |
| 2-4 | 13 | 16.6 | 0 | 0 |
| 4-6 | 31 | 40.4 | 6 | 17.1 |
| 6-8 | 20 | 26.0 | 10 | 28.6 |
| 8-10 | 8 | 10.5 | 5 | 14.3 |
| 10-12 | 2 | 2.6 | 9 | 25.7 |
| Over 12 | 0 | 0 | 5 | 14.3 |
| Totals | 77 | 100.0 | 35 | 100.0 |

the normal and the carcinoma groups, and the distribution curves as shown in Figure 1 were drawn from this table.

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TABLE 2

| Number | Name | Sex | Age | Diagnosis | meg. Lysozyme per ml. whole blood | | |
|--------|--|-----|------|--|--------------------------------------|------|------|
| | | | | | A | B | Mean |
| 1. | I. | F | | Diffuse ca of rectum and bowel | 5.3 | 6.1 | 5.7 |
| 2. | R. | M | | Diffuse ca of bladder and rectum | 15.1 | 15.2 | 15.2 |
| 3. | P. C. | M | | Ca head & eye, 5 yrs. restarted, Ladd serum | 9.95 | 9.95 | 10.0 |
| 4. | M. M. | F | | Ca of the colon | 9.95 | 9.0 | 9.5 |
| 5. | N. H. | F | | Ca of bladder, year ago x-ray, recurrence, Ladd serum | 7.8 | 6.8 | 7.3 |
| 6. | B. S. | F | | Ca of rectum, obstr. of lower urethra | 6.8 | 6.8 | 6.8 |
| 7. | A. S. | M | | Local ca of prostate | 9.6 | 10.4 | 10.0 |
| 8. | G. | F | | Local ca of stomach, post-op. | 11.4 | 10.3 | 10.9 |
| 9. | C. | F | | Ca of cecum | 6.4 | 8.0 | 7.2 |
| 10. | A. F. | F | | Ca of uterus, no treatment | 9.0 | 6.4 | 7.7 |
| 11. | B. | M | | General of prostate | 7.9 | 9.95 | 8.9 |
| 12. | D. P. | F | | | 8.3 | 8.3 | 8.3 |
| 13. | I. G. | F | | Ca of cervix | 11.2 | 11.4 | 11.3 |
| 14. | B. W. | F | — | Post-op. gastro-enter. ca of stomach | 23.6 | 21.2 | 22.4 |
| 15. | G. | F | — | Extensive infiltrated ca of lung, not removed | 10.9 | 10.9 | 10.9 |
| 16. | W. | M | | Local infiltr. ca of chest, not removed | 12.9 | 12.9 | 12.9 |
| 17. | F. | M | | Post-op. ca of bowel extended to bladder | 10.9 | 10.9 | 10.9 |
| 18. | S. | F | | Ca multiple nodules in abdomen and chest | 11.9 | 11.9 | 11.9 |
| 19. | R. G. | M | | Local ca of stomach, post-op. | 11.9 | 11.9 | 11.9 |
| 20. | A. | F | | Ca of colon, Ladd serum | 15.5 | 14.8 | 15.2 |
| 21. | L. | M | | Undiff. ca cervical lymphnodes, primary ca unknown | 13.3 | 13.8 | 13.6 |
| 22. | S. | F | | Ca of uterus with metastasis | 11.4 | 10.9 | 11.2 |
| 23. | E. J. | M | 70 | Ca annular sigmoid obstr. cecostomy; liver metastasis | 9.2 | 9.1 | 9.2 |
| 24. | Z. | M | 48 | Sarcoma thigh, skull, metast. | 4.2 | 4.2 | 4.2 |
| 25. | LeR. G. | M | 53 | Ca of tonsil glands; neck | 4.7 | 5.2 | 5.0 |
| 26. | M. L. | M | 53 | Ca sigmoid metast. to liver; colostomy | 6.4 | 7.3 | 6.9 |
| 27. | A. B. | M | 52 | Complete gastrectomy, metast. liver, etc. | 7.3 | 6.4 | 6.9 |
| 28. | F. S. (greenish-yellow colored plasma) | M | 66 | Ca pancreas, obstr., palp. liver, prob. ca of paner. not yet proven | 8.6 | 7.3 | 8.0 |
| 29. | A. M. | M | 76 | Ulcer mass 3½ in. anus, by biop. only; fixed mass | 7.3 | 7.3 | 7.3 |
| 30. | J. L. | M | 66 | Ca colon, well demon., x-ray | 7.3 | 7.3 | 7.3 |
| 31. | R. H. | M | 43 | Sq. ca thigh from burn; metast. pelvis inguinal reg. | 7.3 | 7.3 | 7.3 |
| 32. | B. | F | | Ca vulva, very extensive | 5.3 | 6.4 | 5.9 |
| 33. | N. A. | F | | Ca cervix, extensive | 8.0 | 6.1 | 7.1 |
| 34. | D. A. (greenish-yellow colored plasma) | F | — | Extensive diffused ca of pelvis, liver metastasis | 4.5 | 4.5 | 4.5 |
| 35. | G. R. | F | | Ca corpus (limited), no meta. | 5.4 | 4.9 | 5.1 |

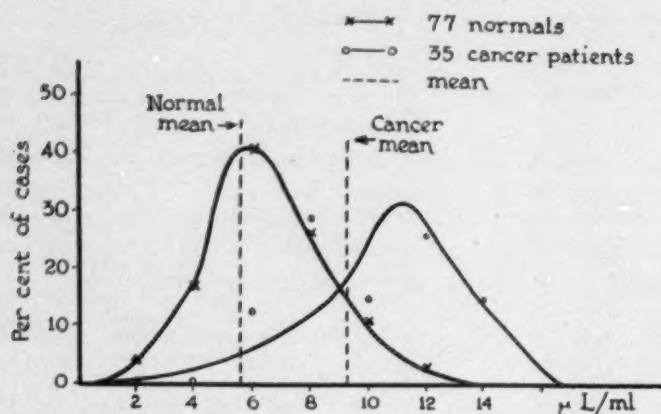


Fig. 1: This figure represents the distribution curves of blood lysozyme activity of 77 normal individuals and 35 patients with localized and/or generalized carcinomatosis. The mean of the control (normal) group was found to be 5.64 mcg. of lysozyme per ml. of whole blood, and that of the carcinoma group 9.26 mcg. of lysozyme per ml. of whole blood. Both means are indicated on the graph.

Comparison of the distribution curves of these two groups shows that a normal curve is obtained for the control group while the curve of the carcinoma group is distorted into the upper limits of lysozyme activity of the blood. The 95 per cent confidence limits for the normal group was calculated to be 1.50 mcg. to 9.70 mcg. of lysozyme per ml. of whole blood; therefore, the mean of the cancer group is not above the upper limits of the normal group. Similarly, the 95 per cent confidence limits for the carcinoma group was calculated to be 7.85 mcg. to 10.67 mcg. of lysozyme per ml. of whole blood.

Table 2 lists the individual patients with the diagnosis and duplicate lysozyme determinations (A and B) of each case. The means of these determinations which were used for the statistical calculations in the text are also listed. Cases one to 22 were patients at Wesley Memorial Hospital and the remaining 13 were patients at Cook County Hospital.

DISCUSSION AND CONCLUSION

The results indicate that patients with localized

and/or generalized carcinoma have statistically a higher blood lysozyme activity which is neither diagnostic nor clinically significant. Attention is, however, directed to the finding that none of the 35 carcinoma patients had less than four micrograms of lysozyme per ml. of blood and that none of the normal individuals had over 12 micrograms of lysozyme per ml. of blood (Table 1). We believe this original observation significant enough to stimulate other investigations to repeat similar studies on larger series of classified carcinoma patients.

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A METHOD FOR THE QUANTITATIVE DETERMINATION OF LYSOZYME ACTIVITY IN BLOOD*

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IN 1922 Fleming (1) reported the presence of a bacteriolytic principle in tears, egg white and other animal fluids which he called lysozyme.

PROPERTIES OF LYSOZYME

Lysozyme is an enzyme which occurs normally in many body fluids. Pure lysozyme preparations are basic in nature, soluble in acidified aqueous media and insoluble in pure organic solvents. Klotz, et al, (2) report an isoelectric point of pH 11 for lysozyme. It is composed of 48.65 per cent of carbon; 6.44 per cent hydrogen, 15.33 per cent nitrogen, 0.25 per cent phosphorus, 0.64 per cent sulphur (as SH) and 3.31 per cent of ash. With phosphorus and sulphur as the basis, its minimum molecular weight should be about 25,000, but this proved to be too high and has recently been reported as 18,000, 15,000 and 14,000 respectively (4, 7). It contains glutamic acid, lysine and other amino acids but is lacking in hydroxyproline or cysteine (5, 6, 8). It has a positive reaction to biuret, glyoxylic acid, Greenberg phenol and nitroprusside (22, 23); the Molish test is negative and bromide in glacial acetic acid is readily decolorized. Precipitation of lysozyme is incomplete by trichloroacetic acid, perchloric acid, sulfosalicylic acid and tungstic acid. Salts of heavy metals precipitate and at the same time inactivate the enzyme.

Lysozyme is very stable toward heat and acid (24). Acidified solutions kept at 100 degrees C. for 45 minutes show no loss of lytic activity while the neutral solutions lose all activity. Nearly all of the activity in a pH 9 solution is destroyed if heated to 100 degrees C. for five minutes. At room temperature treatment with 0.01 N sodium hydroxide for 10 minutes lowers the activity from 3,000 units to 80 units per mg.

Prudden (25) noted a destructive action of peroxides during work with an ordinary vacuum distilled sample of dioxan as a precipitant in which the activity was completely lost. The sensitivity of lysozyme to alkali and peroxide suggested the necessity of an intact sulfhydryl group in the molecule. Iodoacetic acid inactivates the enzyme. The inactivation by iodine and cuprous oxide is partially reversible by hydrogen sulfide. Meyer and his co-workers (3) found that hydrogen cyanide partially reactivated iodine inactivated preparations of lysozyme.

According to Shwachman, Hellerman and Cohn (26) *pneumococcus hemolysin* can be reversibly oxidized and reduced and that the oxidized form is inactive. Meyer (3) also found the same to be true for lysozyme. This suggests the possible role of peroxide in bacteria as a defense against lytic agents. It may also throw

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light on the decreased resistance to infection in avitaminosis A in which it seems to be difficult for the body to maintain substances in the reduced form. The lysozyme content is greatly diminished in the tears of experimental animals and human patients deficient in vitamin A. Keratomalacia disappears following local treatment with lysozyme (24).

Fleming's discovery of lysozyme and his original observations (1) of its lytic activity, either as clear zones on agar plates seeded with *micrococcus lysodeikticus* or as a clearing of a suspension of that same micro-organism, led ultimately to the methods used today in the assay of lysozyme. Bacteria which has been dried under reduced pressure is used in these determinations. The dried bacteria is easily stored and a constant pool of substrate is immediately available by simple rehydration.

METHODS OF ASSAY

The methods of Sandow (10), Goldsworthy and Florey (11) were based on the clearing of cell suspensions of *micrococcus lysodeikticus* with known concentrations of lysozyme. Microscopic observations of lytic activity were made by Rosenthal and Lieberman (12). Boasson (13) developed a technique employing the Mall extinctionmeter using known standards which gave the direct relation of the activity of lysozyme. Smolelis and Hartsell (14, 15) describe a modified quantitative method in which the accuracy was enhanced by the use of crystalline lysozyme. The buffer used in the latter method was modified by us (16) in order to determine lysozyme activity in gastric contents (17, 18, 19, 20) by adding sodium chloride since it was found that chloride ions significantly alter lysozyme activity (15, 16).

The theory of our method is the same as that of the above methods, i.e., if a larger amount of lysozyme is present in a solution, more bacteria will be lysed in the same time interval. An increase of lysed bacteria renders a clearer suspension through which more light will be transmitted. The transmitted light is directly proportional to the lysozyme concentration in the standard or unknown solutions. Five ml. of the standard bacterial suspension (to be described later) added to five ml. of the buffer solution allows about 20 percent of light to pass through, which gives the zero point on the standard curve of the graph.

REAGENTS

M. lysodeikticus (Fleming ATCC 4698) (*) is subcultured on yeast water, veal infusion agar and glucose every 24 hours for three days (14). The last subculture is suspended in M/15 phosphate buffer, pH 6.2, and used to inoculate a large number of Roux or square milk bottles containing the same medium. After 16 hours incubation at 37 degrees C. the micro-organism is harvested in phosphate buffer and exposed

**M. Lysodeikticus* was supplied by the Difco Laboratories, Inc. through the courtesy of H. W. Schoenlein,

to ultra-violet light under standard conditions as described by Smolelis and Hartsell (14). The suspension is shell-frozen and dried under reduced pressure. The resulting yellow powder is stored in the refrigerator (14, 21) and, on the day the assay is to be performed, the cells (**) are rehydrated with chloride phosphate buffer (described below). The suspension is standardized by adjusting to a 10 per cent light transmission in the Coleman spectrophotometer, model 14, using a PC-4 filter and reading at 540 m μ , using a buffer blank.

CHLORIDE-PHOSPHATE BUFFER

The buffer used throughout the procedure contains M/15 Sorenson phosphate buffer, pH 6.2, to which sufficient sodium chloride is added to make a 0.071 N NaCl solution (16). One liter of the final buffer contains 7.42 gm. of KH₂PO₄, 1.755 gm. Na₂HPO₄ and 4.388 gm. of NaCl and distilled water to volume. This solution is stable at room temperature as shown by its pH.

EXPERIMENTAL PROCEDURE

The stock solution of lysozyme contains one per cent crystalline egg-white lysozyme (***) in the chloride phosphate buffer and remains stable for approximately one month under refrigeration.

On the day of the test, five ml. of the stock lysozyme are diluted to 100 ml. with chloride-phosphate buffer. Two standard solutions are prepared as follows: five ml. of chloride-phosphate buffer is added to one ml. of stock solution A and four ml. of chloride-phosphate buffer is added to two ml. of stock solution A. Five ml. of each of these diluted standards are treated in the same manner as the unknown fluids, as described below. This procedure will eliminate possible gross error and will also check on the recovery value to be subtracted from the unknown in those instances where it was found necessary to add more of solution A because of low blood lysozyme activity.

A separate standard curve should be made for each daily preparation of bacterial suspension and also if the room temperature varies more than three to four degrees. Five ml. of the chloride-phosphate buffer is pipetted into each of six cuvettes. Five ml. of the freshly diluted stock solution (A) is added to the buffer in the first cuvette. After thoroughly mixing, five ml. of the contents of the first cuvette is added to the buffer solution in the second cuvette. The process of serial dilution is continued through cuvette #5, mixing thoroughly after each addition. Cuvette #6 containing five ml. of chloride-phosphate buffer is used as the blank control. Five ml. of the adjusted bacterial suspension are then added to each of the six cuvettes at exactly one-half minute intervals and shaken well. After standing for exactly 20 minutes at room temperature, the cuvettes are again well shaken and read in the spectrophotometer at exactly one-half minute intervals. The machine is set to read 100 per cent light transmission with the chloride-phosphate buffer blank in cuvette #6. This procedure permits simul-

taneous determinations of 30 samples with a time lapse of five minutes between the last addition and the first reading when the machine is set.

The standard curve is drawn by plotting the transmission against concentrations of lysozyme. A log scale is used on the abscissa for the concentration.

Three ml. of blood was collected in a syringe which had been lubricated with a little mineral oil and placed in a clean test tube without coagulant. One ml. of blood was pipetted into each of two centrifuge tubes, each containing nine ml. of the chloride-phosphate buffer, for duplicate determinations. These 1:10 dilutions were centrifuged at 27,000 R.P.M. for about eight minutes.

Five ml. of the clear supernatant fluid were placed in another clean test tube or directly into a cuvette, if the lysozyme activity of the blood is sufficiently high to give a final light transmission of between 20 and 70 per cent. This can only be determined by trial and error. If there is a low blood lysozyme activity, one ml. of solution A is added to the five ml. of supernatant fluid. These are mixed well and five ml. are pipetted into a cuvette. Similarly, as for the standard curve, five ml. of the adjusted bacterial suspension are added to the cuvettes, well mixed and allowed to stand at room temperature for exactly 20 minutes before reading in the spectrophotometer.

The per cent of light transmittance is projected on the abscissa of the standard curve and the concentration of lysozyme for each unknown is read. This value, less the amount added due to the addition of one ml. of solution A (if added at all), multiplied by the dilution factor gives the result in micrograms of lysozyme per ml. of whole blood. Using one ml. of solution A, the diluting factor is 12 and 10 if no solution A is added. Theoretically one ml. of the five ml. solution used for the determination contains 0.86 micrograms of lysozyme due to the addition of solution A. Should the blood lysozyme activity be too high for the galvanometer reading, the supernatant fluid, after centrifugation, must be diluted to such an extent as to bring the reading into the proper range. The appropriate dilution factor must then be used to calculate the final results.

RESULTS

The reliability of the method was demonstrated by adding various known amounts of crystalline egg-white lysozyme to whole blood and determining the lysozyme activity by the above procedure. The blood samples were divided into four groups. Group one, to which no lysozyme was added, served as control; 50 mcg of lysozyme were added to group two; 100 mcg. to group three and 200 mcg. to group four.

The lysozyme activity observed in each group is recorded in Table 1 and the range and means of the lysozyme activity are charted in Figure 1. The amount of lysozyme added to the whole blood (mcg. per ml.) is plotted against the lysozyme activity, expressed in mcg. of lysozyme per ml. of whole blood. Each bar represents one group with the lower vertical end of the bar indicating the lowest recovery and the upper vertical end of the bar the highest recovery for its respective group. It is interesting to note that the highest recovery value in group two (containing 50 mcg. of lysozyme per ml. of whole blood) is equal to the low-

** Lyophilized *M. lysodeikticus*, as prepared above, are obtainable from the Difco Laboratories, Inc., Detroit 1, Michigan.

***Difco Laboratories, Inc., Detroit 1, Michigan. Armour Laboratories, Chicago 9, Illinois.

TABLE I

| Group | Micrograms of lysozyme per ml. of whole blood | | | | | | | | | |
|------------------------|---|------|-------|------|---------|-----|-----|-----|------|-----|
| | I | | II | | III | | | | IV | |
| X | 5.5 | 1.8 | 60 | 82.5 | 94 | 89 | 96 | 96 | 223 | 294 |
| | 2.0 | 26.0 | 61 | 57 | 82 | 103 | 94 | 108 | 236 | |
| | 2.9 | 5.8 | 74 | 60.5 | 92 | 106 | 94 | 104 | 254 | |
| | 5.0 | 2.4 | 59 | 63 | 111 | 100 | 111 | 102 | 254 | |
| | 1.8 | 8.86 | 60.5 | | 96 | 94 | 107 | 90 | 264 | |
| | 1.8 | 1.6 | 73 | | 102 | 91 | 95 | 102 | 254 | |
| | 5.5 | 2.5 | 68 | | 90 | 106 | 99 | 116 | 248 | |
| | 2.5 | 4.5 | 76 | | 109 | 112 | 114 | 111 | 270 | |
| | 4.0 | 2.3 | 65 | | 112 | 96 | 114 | | 256 | |
| | 6.5 | 2.3 | 80 | | 96 | 95 | 94 | | 278 | |
| Σ | 95.56 | | 939.5 | | 4117 | | | | 2831 | |
| N | 20 | | 14 | | 41 | | | | 11 | |
| \bar{X} | 4.78 | | 67 | | 100.415 | | | | 257 | |
| mcg. of lysozyme added | 0 | | 50 | | 100 | | | | 200 | |

X—Individual determinations.

Σ —Total of individual determinations.

N—Number of determinations or blood samples in each group.

\bar{X} —Arithmetic mean of each group of lysozyme recovered (Divide the sum total by number of determinations for each group: $\frac{\Sigma}{N}$.)

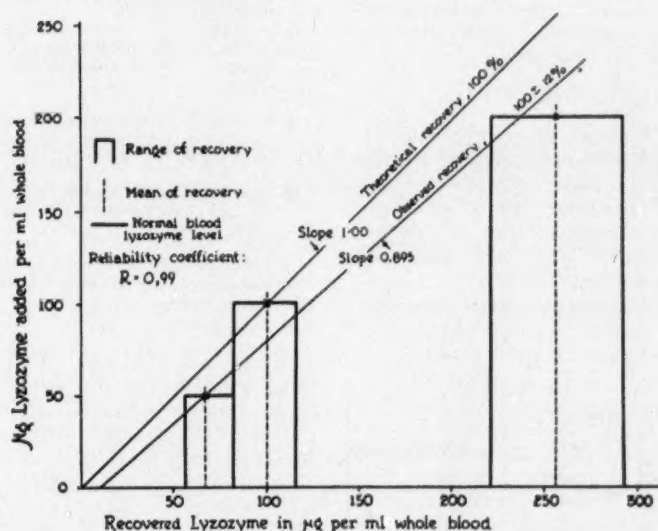


Fig. 1: This graph shows the correlation between crystalline egg-white lysozyme added to whole blood and the lysozyme activity of that blood expressed in mcg. of lysozyme per ml. of whole blood as determined by the method described in the text. The range of recovery is indicated by the vertical lines of the blocks, each block representing a group of blood samples to which various amounts of lysozyme had been added. The mean of each group is indicated by the dotted lines. Theoretical and observed curves are also shown. For explanation see text.

est recovery value in group three (containing 100 mcg. of lysozyme per ml. of whole blood). This indicates quite a spread in each group but is within the ± 12 per cent limit. The means of each group are also indicated by the drawn line which shows theoretical recovery (100 per cent) with perfect correlation. Another line shows the observed recovery using the

means and the normal basal (control) blood lysozyme activity. The resulting straight line constitutes 12 per cent of the theoretical value of the lysozyme added which is satisfactory for this type of test. A statistical evaluation of the results reveals a reliability coefficient of 0.99 indicating almost perfect correlation (1.00) of the amount of lysozyme added and that re-

covered. The reliability coefficient was calculated as follows (by means of the recoveries) :

| x (added) | y (recovered) | x ² | y ² | xy |
|--------------------------|--------------------------|----------------------------------|----------------------|---------------------|
| 50 | 62 | 2500 | 3844 | 3100 |
| 100 | 100 | 10000 | 10000 | 10000 |
| 200 | 252 | 40000 | 63504 | 50400 |
| $\Sigma x = 350$ | $\Sigma y = 414$ | $\Sigma x^2 = 52500$ | $\Sigma y^2 = 77348$ | $\Sigma xy = 63500$ |
| $N = 3$ | | | | |
| $(\Sigma x)^2 = 122500$ | $(\Sigma y)^2 = 171396$ | $(\Sigma x)(\Sigma y) = 144900$ | | |
| $(\Sigma x)^2 = 40833$ | $(\Sigma y)^2 = 57132$ | $(\Sigma x)(\Sigma y) = 48300$ | | |
| $\frac{(\Sigma x)^2}{N}$ | $\frac{(\Sigma y)^2}{N}$ | $\frac{(\Sigma x)(\Sigma y)}{N}$ | | |
| | Σxy | - | | |

$$r = \frac{\sqrt{(\Sigma x^2 - \frac{(\Sigma x)^2}{N})(\Sigma y^2 - \frac{(\Sigma y)^2}{N})}}{\sqrt{(\Sigma x^2 - \frac{(\Sigma x)^2}{N})(\Sigma y^2 - \frac{(\Sigma y)^2}{N})}}$$

$$= \frac{\sqrt{(52500 - 40833)(77348 - 57132)}}{\sqrt{(52500 - 40833)(77348 - 57132)}}$$

$$= 0.99$$

Our method was used to determine the blood lysozyme activity of 77 normal adults. The mean value was found to be 5.64 mcg. of lysozyme per ml. of whole blood with a standard deviation of 2.05 (36.6 per cent), and a standard error of 0.234. A distribution curve was drawn and is shown in Figure 2. Table II presents the data of this part of the experiment.

DISCUSSION AND CONCLUSIONS

The above described bacteriolytic (turbidimetric) method of determining the lysozyme activity in the blood has been proven to be reliable, reproducible and applicable simultaneously to a large number of determinations. A wide range of concentration of crystalline egg-white lysozyme which had been added to whole blood was recovered quantitatively.

An added advantage of the above method is that

TABLE II

| mcg. Lysozyme per ml. Blood | Number of Individuals | Per Cent of Individuals |
|--------------------------------|--------------------------|----------------------------|
| 0-2 | 3 | 3.9 |
| 2-4 | 13 | 16.8 |
| 4-6 | 31 | 40.3 |
| 6-8 | 20 | 26.0 |
| 8-10 | 8 | 10.4 |
| 10-12 | 2 | 2.6 |
| Totals | 77 | 100.0 |

This table shows the number of individuals falling into certain ranges of lysozyme activity. It can be seen that about 40 per cent fall into the range of 4-6 mcg. of lysozyme per ml. of whole blood where the peak of the distribution curve appears.

the results are expressed in metric units of crystalline lysozyme in contrast to varying units previously utilized by different investigators. Our unit measure facilitates inter-laboratory comparison without the necessity of laborious conversions.

The authors wish to express their gratitude to Mrs. Elizabeth Potter for her very able technical assistance.

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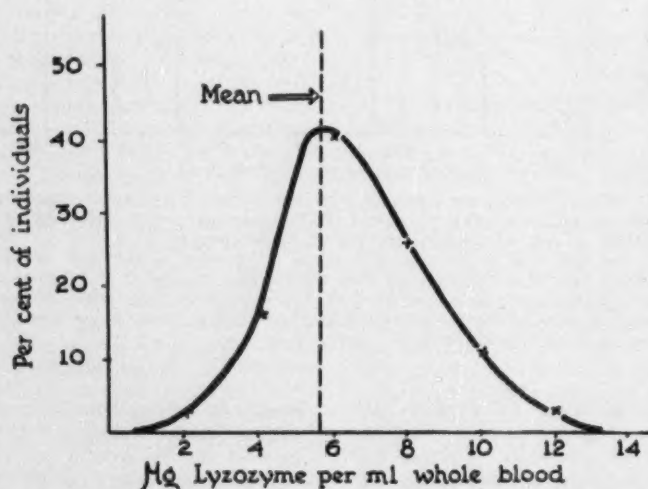


Fig. 2: This figure represents the normal distribution curve of blood lysozyme activity of 77 patients. The mean, as indicated on the graph, was found to be 5.64 mcg. of lysozyme per ml. of whole blood.

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ABSENCE OF DEGENERATIVE CHANGES 20 YEARS AFTER DIABETIC COMA WITH A BLOOD SUGAR OF 1850

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IS IT possible to have the onset of diabetes in a coma with a blood sugar of 1850 mg. per cent and a CO₂ of 13 volumes per cent and 20 years later still be free of any evidence of vascular degeneration?

Is it possible for a diabetic to have multiple pregnancies; to be subjected to numerous major surgical procedures and the anesthetics incident to these operations; to be subjected, also, to various infections like lobar pneumonia, abscesses, pelvic inflammatory disease, and pyelonephritis, and still, at the end of 20 years, be free of any evidence of vascular degenerative changes?

And finally, is it possible to have diabetes for 20 years, and during that time permit the post-prandial blood sugars (1, 2) to average over 200 mg. per cent most of the time, and frequently go up to 300, and

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NOVEMBER, 1954

even 398 and 432 and 540, with no regard for any glycosuria (3) that might occur, and still find no evidence of vascular changes by any of the accepted methods of detection employed today?

The authors herewith present a case history to show that not only can each of these possibilities occur, but have actually all happened in a single patient whose course they have been following for 18 of her 20 years as a patient in the Metabolic Clinic of the Philadelphia General Hospital, with 17 ward admissions during that time.

REPORT OF A CASE

The first admission of this single, colored female, N. D., age 21 years, to the Philadelphia General Hospital was on June 21, 1934. At this time, there was no reason to suspect diabetes, nor was there any evidence of it in the routine laboratory studies done on admission. Six days later she gave birth to a normal, live, female child, weighing 8 lbs., 7 oz.

Family history revealed that the patient was an illegitimate child whose paternal family history was unknown. Her mother, who died at the age of 59 was not a diabetic. She gave birth to six children. (One, the patient's brother, was diagnosed as a diabetic in 1948. He became the father of five children, all living and well at the time of this report.)

The second admission of this patient was five months later, on December 23, 1934, when she was brought into the hospital in a stuporous condition by some member of the family, who volunteered the information that the patient had been well until one month prior to admission. About that time she developed increased thirst and weight loss, followed in about two weeks by increasing weakness and anorexia. Admission chemistry studies gave the following values: blood sugar, 1,850 mg. per 100 cc.; blood urea nitrogen, 95 mg. per 100 cc.; carbon-dioxide combining power, 13 volumes per cent; hemoglobin, 16.8 gm. per 100 cc.; white cells, 12,700 per cubic millimeter, with 76 per cent neutrophils and 24 per cent lymphocytes; plasma cholesterol, 170 mg. per 100 cc., with esters, 82 mg. or 48 per cent.

The patient, admitted to the Metabolic Ward, was given the usual intensive coma treatment. By 7 P. M., after 280 units of regular insulin had been given, the blood sugar was 1,550 mg. per 100 cc., and the carbon-dioxide combining power was still 13 volumes per cent. Treatment was continued, and by 8 A. M. the blood sugar was 488 mg. per 100 cc., and the carbon dioxide combining power, 56 vol. per cent, and the urine negative for sugar and acetone. The blood pressure which had been 30/0 on admission, was now 86/34.

Several days post-coma the patient developed signs of lobar pneumonia, which although atypical in its course, finally resolved, and the patient was discharged February 1, 1935 on 10 units of regular insulin once daily.

The third admission to the Metabolic Ward of the Hospital occurred September 19, 1935, with the diagnosis of Acute Pelvic Inflammatory Disease. Recovery was rapid, and the patient was discharged September 30. During this stay her weight was 122 pounds; her blood sugar varied from a high of 326 to a low of 78 mg. per 100 cc.; eye consultation reported normal fundi; and the insulin dose at time of discharge was 31 units of regular insulin in divided doses.

The fourth admission was on October 2, 1935, again with Acute Pelvic Inflammatory Disease. Weight was 119 pounds; fasting blood sugars fluctuated between a high of 202 and a low of 60 mg. per 100 cc.; eye grounds were again reported normal; chest x-rays were negative; gall-bladder x-ray studies were negative; and urinalysis was negative except for a very faint trace of albumin. Patient was discharged October 19, on an insulin dose of 20 units regular insulin.

The fifth admission was on February 28, 1938, this time for re-standardization and for an Ascheim-Zondeck test for determination of pregnancy or a dead fetus. The test was unsuccessful because the animal died. X-ray of the abdomen failed to show the fetus. Fasting blood sugar was 174 mg. per 100 cc. and post-prandial blood sugar was 260 mg. per 100 cc. Eye ground examination and electrocardiogram were both negative. Patient was discharged March 12, on 20 units regular plus 10 units protamine zinc insulin.

The sixth admission was on June 3, 1938, at age 24, this time to the Maternity Ward. On June 9 she spontaneously delivered a premature living female child (estimated date of confinement was August 8), weighing 4 lbs., 1½ oz. Diet at the time consisted of

60 gm. protein, 130 gm. fat and 140 gm. carbohydrate. Urinalysis was negative. Insulin requirement, which was up to 45 units regular plus 18 units protamine zinc insulin just before delivery, fell to 47 units of regular insulin at time of discharge June 28. Fasting blood sugars ranged from a high of 284 to a low of 55 mg. per 100 cc. (This child died at 6 months of age of pneumonia).

The seventh admission occurred July 5, 1939, this time for a subcutaneous areolar tissue abscess and paronychia of the index finger of the left hand. The distal phalange of this finger was amputated July 13. She was discharged July 17, on 38 units regular and 20 units protamine zinc insulin.

The eighth admission was for abdominal pain, nausea and vomiting, on January 11, 1940. Symptoms subsided rapidly and patient was discharged in 24 hours. Fasting blood sugars were 292 and 200 mg. per 100 cc. Discharge dose was 53 units regular plus 20 units protamine zinc insulin.

The ninth admission was on December 12, 1940, for acute gastroenteritis. A normal appendix was removed December 13. Urinalysis was negative. Blood sugar range was from 312 to 88 mg. per 100 cc. fasting, and from 350 to 74 mg. per 100 cc. post-prandially. She was discharged December 24, on 25 units regular plus 15 units protamine zinc insulin.

The tenth admission was on June 12, 1942, for vaginitis due to *Monilia* infestation and for re-standardization of uncontrolled diabetes. The diet was changed to 80 gm. protein, 100 gm. fat, and 200 gm. carbohydrate. Electrocardiogram was normal. The fasting blood sugars ranged from 232 to 170 mg. per 100 cc., and post-prandially from 350 to 122 mg. per 100 cc. She was discharged June 20, on 34 units regular plus 15 units protamine zinc insulin.

The eleventh and twelfth admissions, September 1 to September 16, 1944, and September 21 to October 6, 1944, were both for nausea and vomiting of early pregnancy. Eye ground examination, electrocardiogram, and chest x-ray were all normal. Fasting blood sugars ranged from 298 to 76 mg. per 100 cc., and post-prandial blood sugars ranged between 380 and 194 mg. per 100 cc., with one insulin reaction when the blood sugar dropped to 65 mg. per 100 cc. Discharge dose on October 6 was 15 units regular and 32 units protamine zinc insulin.

The thirteenth admission was on December 9, 1944, for pregnancy and polyhydramnios. January 29, 1945, while in the hospital, the patient developed bronchopneumonia, which responded to Sulfamerazine. Eye ground studies and electrocardiogram were both normal. On February 15 she was delivered of premature live twins by the normal route, one weighing 4 pounds, 8 ounces, the other 4 pounds, 14¾ ounces. One of the twins died shortly after discharge from the hospital, the other about a year later, the cause in each being unknown,—the mother does not remember. Fasting blood sugars during this admission ranged between 398 and 44 mg. per 100 cc., while post-prandial blood sugars ranged between 429 and 96 mg. per 100 cc.

The fourteenth admission, March 31, 1948, was for cystocele, rectocele, and prolapse of the uterus. On

April 13, 1948, an anterior and posterior colporrhaphy was done under spinal anesthesia. This healed by second intention because of superficial disruption and infection of the perineorrhaphy incision. The fasting blood sugar range was from 287 to 71 mg. per 100 cc.; the post-prandial blood sugar was 204 mg. per 100 cc. Patient was discharged April 30 on 35 units globin insulin with breakfast and 20 units globin insulin with supper.

The fifteenth admission, July 5 to July 7, 1949, was for tonsillectomy.

The sixteenth admission was on March 11, 1953, for a diabetic ulcer of the right great toe. This healed on conservative therapy. Urinalysis was negative. Fasting blood sugars ranged from 234 to 78 mg. per 100 cc., and post-prandial blood sugars ranged between 432 and 173 mg. per 100 cc. Patient was discharged March 16, 1953, on 25 units globin plus 25 units regular insulin.

The seventeenth admission of our patient, now 40 years old, was on September 21, 1953, for pregnancy, shortness of breath, and swollen feet. Dyspnea and occasional nausea and vomiting began about two months before admission, and the ankles began to swell two days before admission.

Physical examination revealed a well developed, well nourished, colored female; pulse rate, 78 per minute; blood pressure, systolic 128, and diastolic 72. Physical findings were essentially negative except for evidence of an approximately seven month pregnancy. Laboratory studies on admission revealed a fasting blood sugar of 199 mg. per 100 cc., post-prandial blood sugar of 262 mg. per 100 cc., blood urea nitrogen, 11 mg. per 100 cc.; carbon-dioxide combining power, 43 volumes per cent; hemoglobin 12.0 gm. per 100 cc., and serology was negative. She was taking 23 units globin insulin with breakfast.

On September 25, the patient's blood sugar went to 540 mg. per 100 cc., and the carbon-dioxide combining power to 11 volumes per cent. She responded well to intensive therapy, although the carbon-dioxide combining power remained in the thirties throughout the remainder of her pregnancy. From September 25 to November 19 (date of delivery), patient was maintained on divided doses of regular insulin, taking up to 100 units a day on October 2, and then gradually requiring smaller doses, until she was changed to globin insulin the day after delivery, and was discharged November 30 on 15 units globin insulin once daily.

Although no endocrine studies were made, the patient was given 25 mg. stilbestrol four times daily.

On October 5, x-ray revealed the presence of a twin pregnancy, and on October 14, x-ray was still unable to visualize the distal femoral epiphyses, so that fetal age could not be determined radiologically.

On October 10 the patient developed pyelonephritis, which was treated with antibiotics. A post-therapy specimen of urine, obtained November 19, revealed no pyuria and a negative culture.

Ophthalmoscopic examination revealed normal fundi. A neurologic consultant found no organic pathology, although for some reason not stated he thought

that the patient might have some diabetic neuropathy. Several electrocardiograms were done, all normal. X-ray examination of the lower extremities revealed no bony abnormality and no evidence of vascular sclerosis.

Patient went into labor November 19, and was transferred to the Maternity Ward. She was delivered of twins the same day, the first spontaneously and the second by breech extraction. An episiotomy and repair were done. Both infants were living and premature, one weighing 3 pounds, 14 ounces, the other 4 pounds, 8 ounces. The one that delivered spontaneously showed cyanosis of the head and died 6 days later of congenital atelectasis. The other child was living and well at the time of this writing.

The patient was transferred back to Metabolic Ward, where her post-partum course was uneventful, except for some mild vaginal bleeding. Her hemoglobin fell to 7.8 gm. per 100 cc., and she was transfused and started on iron therapy. She was discharged November 30, to be followed in Metabolic and Post-natal Clinics.

DISCUSSION

How high can a blood sugar get and still not cause irreparable damage? How many complications can a diabetic suffer and still not show any serious consequences? How long can a person have diabetes and still escape vascular degenerative changes as measured by our present day methods? These and many similar questions are frequently asked of any doctor who has one or more diabetics under his care. And the answers are not easy. With all we have learned about diabetes to date, we still have no unanimity of opinion on what causes the vascular degenerative changes so commonly associated with diabetes. Some will tell you that the so-called "diabetic complications" are caused by poor control, inadequate insulin dosage, high blood sugars. Others, just as learned and just as sincere, will tell you that it is not so much the size of the insulin dose, nor even the degree of glycosuria nor hyperglycemia that are the deciding factors, but rather it is the duration of the diabetes that is the determining factor in the causation of vascular degeneration.

The authors have discussed this problem at great length in their paper entitled *Compatible Hyperglycemia* (5), and after very extensive studies, came to the conclusion that the true etiology of premature arteriosclerosis in diabetes is still unknown. The results of their statistical and clinical survey revealed that the apparent known duration of diabetes plays no role in the incidence of vascular complications, that there is no relationship between blood sugar levels and these complications, and that there is no relationship between the average insulin dose and "vascular complications." They concluded that there exists no statistically significant necessary relationship between the control of diabetes and vascular degeneration; that the control of glycemia does not check the progress of vascular degeneration (6, 7, 8), yet one can have diabetes of long standing without necessarily resulting in severe atherosclerosis (9). In fact, contrary to the general belief that hyperglycemia is harmful, compatible post-prandial hyperglycemia was observed to be protective (5).

The authors do not mean to prove their theory con-

cerning compatible post-prandial hyperglycemia with the presentation of this case. Their methods and the reasons for these methods were very thoroughly covered in previous papers (1, 3, 5, 10). With the barrage of claims and counter-claims as to the one "best" way to treat diabetes and avoid its concomitant vascular degenerative changes, it would be as misleading for the authors to say "post hoc ergo propter hoc," as it is for others to infer what they do when, for example, they say that diabetic patients successful in avoiding glycosuria and hyperglycemia often do not develop retinopathy (11). Rather, a thorough survey of the literature on this subject is more apt to leave one with an open mind, and to agree with Pillow and Palmer (12) when they conclude that no explanation can be given for the absence of extensive premature vascular disease in poorly controlled diabetes of long duration and its presence in well controlled cases of diabetes of shorter duration.

CONCLUSION

As presented here, this case demonstrates that diabetes can be of long duration, can at times be unusually severe, can be complicated by severe coma, (with the highest recorded blood sugar with survival in the world's medical literature), and by various infections (pneumonia, abscesses, pyelonephritis, pelvic inflammatory disease), and can be subjected to the strain of many surgical procedures and of multiple pregnancies, yet can escape the vascular degenerative changes usually associated in the minds of many with diabetes that has been under other than constant normoglycemic control.

It is noted that for more than 15 years of the 20 years that this patient was known to have diabetes, she was being treated according to the method of compatible hyperglycemia as described by Sindoni, Ger-

ber, Bove and Zibold (5), using post-prandial blood sugars as the guide to therapy.

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FALSE POSITIVE FREI TEST

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THE FOURTH venereal disease, now called lymphogranuloma inguinale, is rarely seen in this area. When suspected, the Frei test is invariably employed and great reliance placed upon it. One of the associated conditions is the rectal inflammation leading to marked thickening and stricture and so simulating malignant disease. The proctitis may occur with very little associated change in the inguinal lymph nodes. The Frei test is generally regarded as conclusive but as with all biological methods, it may be in error and its limitations must be recognized. The case herein reported is from the service of the late Dr. Leslie Sullivan and illustrates a positive Frei test in a case of rectal carcinoma demonstrated by biopsy and subsequent surgery.

CASE REPORT

Mrs. M. S. White, 49 years of age, housewife, native to this area and happily married, when seen in May 1942 complained of pelvic pain of several months

The Ellis Hospital Laboratory, Schenectady, New York.

duration and slight rectal discharge of blood-tinged mucus. Digital and proctoscopic examination disclosed a constricting rectal lesion. There was no history of a primary sore and both Wassermann and Kline tests were negative.

In 1922, she had an operation for piles since which time there had been constipation and ribbon stools. In 1932, bowel movements became painful and a somewhat purulent rectal discharge appeared. To relieve this condition her rectum was stretched. On May 20, 1942 profuse rectal bleeding took place and at this time she was seen by Dr. Sullivan in his office who on rectal examination found a tubular constriction reached by the tip of the finger. As part of the general examination a Frei test was done using chick embryo antigen intradermally and read as strongly positive in 48 hours. There was a dark red wheal 2.0 cm. in diameter as shown in the photograph. The antigen control was negative. A few days later a rectal biopsy was reported as epidermoid carcinoma.

On June 3, 1942, a laparotomy by Dr. F. F. Mc-

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Fig. 1: Photograph showing positive skin reaction.

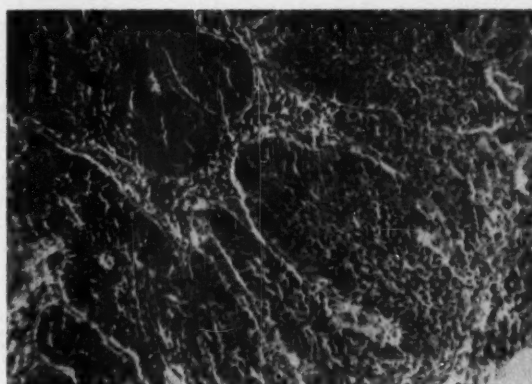


Fig. 2: Photomicrograph of tumor of rectum. X 270.

Gauley revealed the rectum as a hard tubular mass fixed to the sacrum and many metastatic nodules in the liver. A double-barrel colostomy was made. Subsequently, obstructive symptoms developed and in January, 1943 led to the removal of 30 cm. of ileum showing considerable peri-inflammation apparently due to sulfanilamide crystals. A lateral anastomosis was made. In March, 1947, because of pain and rectal bleeding she was admitted for radiotherapy. At this time rectal tissue removed was reported as epidermoid carcinoma, non-cornifying. This tissue and that removed originally were similar in appearance. She died October 28, 1947, at home. An autopsy not obtained.

The Frei test was devised in 1925 (1) and the antigen prepared by diluting the bacteria-free pus from a known case of lymphogranuloma inguinale. Following intradermal injection, an erythematous papule measuring up to 2.5 cm. in diameter formed after 48 hours and persisted for several days. Subsequently, the antigen was prepared in other ways as from chick embryo and mouse brain.

The test is regarded as highly specific and earlier writers stated that false positives were "almost unknown." Later on it became apparent that false positives do occur but could be checked by the use of non-virous antigen tissue control and the complement fixation test. The specificity of the test was challenged in 1943 by Knott et al (2) and several reports of false

positives have been made. In addition cross reactions with certain viral diseases are known. Curth (3) found false positives in control cases when using yolk sac antigen. Binkley, Lane et al (4) found many false and doubtful reactions. Even Frei (5) cautioned against false reactions in the use of the "inverted test"—injecting the patient's pus into a known case of lymphogranuloma inguinale.

This brief report illustrates the limitation of the Frei test and the importance of biopsy.

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ABSTRACTS ON NUTRITION

RYER, R., GROSSMAN, M. I., FRIEDEMANN, I. E., BEST, W. R., CONSOLAZIO, C. F., KUHLE, J., INSULL, W., HATCH, F. T. and the Staff of the U. S. Army Medical Nutrition Laboratory: *The effect of vitamin supplementation on soldiers residing in a cold environment.* *J. Clin. Nut.* 2, 3, May-June 1954, 179-194.

In a study of 2 groups of soldiers, one supplemented with high doses of vitamins of the B complex and ascorbic acid, and the other receiving placebos, the following observations were made: there were no

significant differences between the 2 groups in regard to urinary nitrogen excretion, blood glucose, hemoglobin, creatinin excretion and 17-ketosteroid excretion. Urinary and blood ascorbic acid showed the expected differences between the two groups, with very high volumes in the supplemented group. During cold exposure both groups showed increased excretion of oxidized ascorbic acid. The fall in eosinophil count during forced marches was greater in the supplemented group, and the same group showed greater fall in body weight during the experiment. Psychologi-

cally, no differences could be found between the two groups.

COLLENS, W. S.: *Regulated versus free diet in the treatment of diabetes mellitus*. J. Clin. Nutrition, 2, 3, May-June 1954, 195-203.

Collens goes over the arguments for and against free dieting in diabetes. As is well known, Banting favored allowing the patient to eat what he wanted, provided the right dose of insulin was struck. Collens quotes from a letter from Banting, in which this very attitude was shown. Tolstoi's work is referred to. However, in conclusion, Collens favors a regulated diet and careful insulin coverage to control both blood and urinary glucose. One of his best arguments is that glycosuria produces dehydration with loss of electrolytes. Another is that glycosuria often produces vulvar irritation. He stresses the need of further knowledge with respect to the late degenerative changes.

BANERJEE, N.: *The place of intravenous iron administration in combatting anemia during deep x-ray therapy*. J. Indian Med. Assn., 23, 10, July 1954, 436-441.

The author used intravenous, saccharated iron in anemic patients with malignant disease who were treated by deep x-ray by wide-field application. Iron so given appeared to check the anemia so frequently made worse by deep x-ray, and permitted the patients to finish up their course of x-ray treatment. He found the anemia usually was of the hypochromic, microcytic type. Iron therapy was of no value in malignant obstruction of the esophagus. Occasional febrile reactions to the injections were seen. The iron should be injected very slowly.

STAMLER, J., PICK, R. AND KATZ, L. N.: *Estrogen prophylaxis of cholesterol-induced coronary atherogenesis in chicks given adrenal corticoids or A.C.T.H.* Circulation, X, 2, Aug. 1954, 247-250.

Estrogen prophylaxis of experimental cholesterol-induced coronary atherogenesis in cockerels is unimpaired by the hyperadrenalism and steroid diabetes variously produced by concomitant exhibition of desoxycorticosterone (D.C.A.), hydrocortisone, cortisone or A.C.T.H.

STAMLER, J., PICK, R. AND KATZ, L. N.: *Inhibition of cholesterol-induced coronary atherogenesis in the egg-producing hen*. Circulation, X, 2, Aug. 1954, 251-254.

Mature, egg-producing hens, intact or after oviduct ligation, are remarkably resistant to cholesterol-induced coronary atherogenesis. The inhibition of coronary atherosclerosis is apparently effected by endogenous estrogen secretion by these female birds.

BEST, M. M., DUNCAN, C. H., VAN LOON, E. J. AND WATHAN, J. D.: *Lowering of serum cholesterol by the administration of a plant sterol*. Circulation, X, 2, Aug. 1954, 201-206.

The plant sterol, beta-sitosterol, was administered to 9 subjects on unrestricted diets. A sustained reduction

of serum total cholesterol and a lowering of the ratio of cholesterol to lipid phosphorus occurred. Interference by sitosterol with the absorption of cholesterol, both dietary and that excreted into the gastro-intestinal tract, is presumably responsible for this hypocholesterolemic effect. No toxic side effects were observed. A means of studying the effects of a sustained lowering of serum cholesterol on atherosclerotic states would now seem to be available.

STAMLER, J., PICK, R. AND KATZ, L. N.: *Effects of cortisone, hydrocortisone and corticotropin on lipemia, glycemia and atherogenesis in cholesterol-fed chicks*. Circulation, X, 2, Aug. 1954, 237-240.

Hydrocortisone markedly affected carbohydrate, protein, lipid and electrolyte metabolism of cholesterol-fed cockerels (intact, alloxanized and depancreatized). Despite steroid-induced diabetes and hyperadrenalism, associated with enhancement of hypercholesterolemic hyperlipemia, no hypertension or intensification of atherogenesis (aortic or coronary artery) supervened. A.C.T.H. produced similar effects. Cortisone was relatively inactive as a glucocorticoid in this avian species. Despite its slight metabolic activity, it moderately elevated blood pressure and intensified atherogenesis.

DOIG, R. K., TURNBULL, A., BADENOCH, J., MOLIN, D. L. AND ROSS, G. I. M.: *Discussion: gastric biopsy and the investigation of the megaloblastic anemias*. Proc. Roy. Soc. Med., 47, 6, June 1954, 423-431.

Gastric biopsy is a simple, safe technique by which an adequate and representative sample of the gastric mucosa can be obtained. The histological appearance may be normal, or may show a superficial or atrophic gastritis, or gastric atrophy. Half of the patients with gastritis had a recognizable clinical story of indigestion. Gastric atrophy was almost always found in patients with pernicious anemia or subacute combined degeneration of the cord and the gastric lesion was not affected by treatment.

Giving cobalt labelled vitamin B₁₂ to normal persons resulted in a recovery of 30 percent in the feces. In patients with pernicious anemia in remission, the amount recovered in the feces was between 80 and 95 percent, showing that the tissues already were saturated by injections. In persons following total gastrectomy very high amounts were recovered in the feces unless a source of intrinsic factor was given with the test dose of labelled vitamin. The method apparently is useful in determining the presence or absence of intrinsic factor secretion.

The examination of blood serum for the presence of vitamin B₁₂ indicates that persons having 100 micro-micro-grams per ml. or less, are deficient, even though not a few of these show no evidence, as yet, of anemia. In subacute combined degeneration of the cord, low blood readings are found. In fact, such readings assist greatly in differentiating S.C.D. from multiple sclerosis or other neurological conditions. Such blood examinations are also of value in relatives of patients with pernicious anemia, in vegetarians and in patients following gastrectomy. Even though the blood level of vitamin B₁₂ may be found low, no anemia may appear for one or two years.

WILGRAM, G. F., HARTROFT, W. S. AND BEST, C. H.: *Dietary choline and the maintenance of the cardiovascular system in rats*. Brit. Med. J., July 3, 1954, 1-5.

Young rats fed diets low in choline developed cardiac changes which were initiated by the deposition of stainable fat droplets in the myocardium and which rapidly developed into widely distributed focal areas of frank necrosis. Choline prevented the accumulation of significant deposits of fat and the development of cardiac necrosis. These findings suggest that adequate supplies of lipotropic factors may be necessary for the maintenance not only of a healthy liver but also of normal cardiovascular and renal systems in the rat. The term "lipotropic" should be made to include prevention of abnormal fat deposits in all organs of choline deficient animals in which it has been demonstrated

that this result is the direct outcome of lack of choline and its precursors.

O'BRIEN, J. R.: *Is liver a "tonic"? A short study of injecting placebos*. Brit. Med. J., July 17, 1954, 136-137.

Liver extract, vitamin B₁₂ and normal saline, all disguised to look alike, were injected into 4 groups of patients, totalling 86 subjects, 227 injections being made. Briefly, no tonic effect could be noted which was any more pronounced in the case of liver or vitamin B₁₂ than in the case of saline injection. The reported tonic effect of such injections would seem to be due to the suggestibility of the patient receiving them. Women appeared more suggestible than men. Blood counts were not made, and opinions were based on the answers to a number of questions such as, "Are you more energetic?"

EDITORIALS

THE "LONG THINS"

About 20 years ago it was customary to treat run-down, viscerototic individuals by bed rest in hospital, with forced nutrition, and by means of elevating the foot of the bed. Sometimes poor results were obtained. However, many of these patients, provided they could remain in hospital for many weeks, or even months, put on weight and gained strength. In some of them, this form of treatment marked the beginning of a long period of health.

Gradually the idea of resting in bed for weeks for this modified Wier-Mitchell treatment became unpopular and finally abhorrent to the patients, so that, today, it is unusual to attempt to use such treatment in spite of its advantages. The reason for such unpopularity is partly economic, and partly the general concept of movement which has taken hold of medicine as well as the public. The most unpalatable medicine today is rest.

Actually the writer has never obtained the much-needed gain in weight by any method except prolonged rest and forced nutrition. There is no more miserable group than the viscerototics with their well-known train of symptoms of weakness, indigestion and inefficiency. We note with interest that Garfield G. Duncan, M.D., of Philadelphia, has returned to this form of treatment with excellent results.

1. Duncan, G. G.: Some considerations of Nutrition in General Practice. New Zealand M. J., 53, 294, April 1954.

A CRITIQUE ON CURRENT MEDICAL EDUCATION

Medicine has become more skilled, more specialized and more impersonal. This criticism is not valid unless it might apply to the case where the general practitioner attempts to diagnose his case by sub-specialist consultations, rather than sending it to the internist in the first place.

This is the crux of the situation. The medical schools and the incumbent professors of medicine seem to feel

that their school's prestige is best advanced by sub-specialists, primarily doing research, a little teaching and some consulting.

The sub-specialist is very necessary and by his contributions, can raise the standard of medical education. However, I believe the broad internist who has spent a certain period of time under various sub-specialists is better qualified to carry the bulk of the teaching burden. His is the task to integrate, coordinate, and interpret the results of the sub-specialist's findings. He is the natural leader of the team and is far ahead on the question of judgment, and the personal relationships involved.

It would seem obvious that certain medical schools are better qualified to prepare their students for graduate study. The endowment which attracts an excellent faculty in ability and breadth of scope is important. It surely should attract the better students, though financial problems may cause an excellent student to stray.

The general practitioner is basic in the system of American medical practice. The bad publicity that seems to have rubbed off on many of them, has caused the group as a whole, to lose sight of the fact that they learn by consultation. When their diagnosis is confirmed, it adds to their prestige, and early consultation saves serious difficulty even if another diagnosis is arrived at. The busy general practitioner has no time to spend hours in the hospital even if he had the training demanded by present day standards.

Most internists make it a practice to render a full written report on the patient's course and progress in the hospital and are satisfied with one follow up visit, then the patient is returned to the family physician. It is only in a difficult therapeutic problem that the internist follows the patient along, and this only at the desire and in cooperation with the general practitioner. The best advice to a patient is to select a physician doing general practice in the vicinity of his residence whom he likes and has confidence in. This physician is to be consulted first at all times. However,

any patient who feels he is not improving or desires another opinion could consult a broad internist who in turn would render a report to the family physician.

The Academy of General Practice has done a remarkable job in reviving interest in general practice and in furthering graduate study. Yet, in a metropolitan center there appears to be little need for a section on general practice in hospitals. The American Medical Association is cognizant of the problem and ruled that such a section is an administrative function only with some support to the out-patient department. Certainly, physicians that have spent many additional years in training are better geared to the needs of hospital practice. The general practitioner is invited to follow the patient's course and record in the hospital. This is the best post graduate training available.

The problem in a large eastern city is that the young internist is only paid a pittance by a medical school that would like a half day of his time every school day. Consequently, he must work for an older physician with a large established practice or take an industrial position if he wants to do internal medicine only. The other alternative is to establish an office in a community and do limited general practice. This is cer-

tainly not the best way to keep abreast of medicine today.

Now the medical schools could improve the status of the young internist especially if the surgeons were willing to equalize earning power. The training and ability of a wide internist matches or excels a fine general surgeon. The Blue Shield plan so far has neglected this aspect and from the comments and letters submitted will soon take steps to remedy the defect of their own early experience.

It is said, "to understand the role of the physician in any age is to understand the culture of the period." The preeminence of the internist is recognized and accepted by all. He is in short, the personal physician among all the sub-specialists. By training, experience, and a philosophy or mental discipline, the internist is best equipped to understand and interpret the implication of medical activity on man's welfare. Therefore, a fervent plea is expressed, that medical schools apportion the bulk of the clinical teaching to the broad internist and revive their interest in the development of physicians of that caliber.

Edward S. McCabe, M.D.,
Philadelphia, Pa.

BOOK REVIEWS

A DEVOTION TO NUTRITION. Frederick Hoelzel, Vantage Press, 120 W. 31 St., New York 1, N. Y. 1954. \$2.50.

Hoelzel has been associated with Prof. A. J. Carlson for many years in physiology, and this journal has published a number of his contributions to Nutrition. It is unlikely that anyone else in the world, possessing the same knowledge of physiology, has ever used himself, as a guinea-pig, so consistently and over so very long a period of years, for self-experimentation in nutrition. For many years his leading interest lay in the effects of periodic semi-starvation and what is of unusual interest was Hoelzel's point of view. Originally with a religious background, he switched over to scientific pursuits, but he never quite lost the idea or hope that, through restricted diets, he could eventually accomplish unusual strength and clarity of mind. In fact, it appears that on many occasions, during and following fasts of various lengths, he actually experienced new vigor of body, mind and soul. On the whole, however, Hoelzel today feels that there is a definite limit to the advantages to be obtained from

restricted diets. Such diets do not prevent the evidences of aging. The remarkable "spurts" of physical and mental energy which he experienced following periods of fasting were, he believes, due to stress-stimulation of the A.C.T.H.

While the volume seems to be written for the public, it also affords unusual interest for the physician.

STUDENT'S GUIDE IN NURSING ARTS. M. Esther McClain, R.N., M.S. The C. V. Mosby Co., St. Louis, 1954, \$3.00.

The Third Edition of this volume represents a complete revision and reorganization of the material presented. It is a practical question-and-answer type of text which gives the student nurse orientation to hospital nursing, the care of the patient in the hospital, the nature of the patient's needs, the making of a diagnosis, general modes of treatment and the patient viewed as an individual. The book conforms to the author's "Scientific Principles in Nursing" and will prove most valuable to teachers of nurses who desire an outline for the course of studies.

GENERAL ABSTRACTS OF CURRENT LITERATURE

ROSSER, J. H. AND McCALL, R. A.: *Persistent postoperative common duct stones and their non-operative management*. U. S. Armed Forces M. J., V. 5, May 1954, 658-666.

The 15 percent average incidence of choledochal stones persisting after exploration of the common bile

duct for calculi presents the surgeon with a problem in management. Three non-surgical techniques are recommended to treat the complications successfully, making secondary operations on the common bile duct less necessary: (1) Pribram's ether method; (2) Best's three-day biliary flush; and (3) paralysis of sphincter

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of Oddi by direct application of a topical anesthetic agent. In a case report exemplifying the use of 2 percent procaine hydrochloride to anesthetize the sphincter, sterile saline solution under pressure washed the retained common duct stones into the duodenum. The literature contains many other case reports establishing the worth of these three nonoperative means of eradicating calculi remaining after common duct exploration for choledocholithiasis.

HENDRICKS, A. B.: *Liver biopsy in diagnosing hepatomegaly*. Miss. Valley Med. J., 76, 3, May 1954, 115-119.

Biopsy of the liver affords a direct approach to accurate diagnosis of hepatomegaly. The punch biopsy technique with the Vim-Silverman needles is of great value at the operating table or at the hospital bed-side. The information obtained with the biopsy correlated with the clinical and biochemical picture clarifies many cases of hepatomegaly. The complications are few and the mortality rate from the procedure is negligible. Liver biopsy, however, is not an office or out-patient technique.

WILLIAMS, G.: *Acute pancreatic necrosis as a cause of sudden death*. Brit. Med. J., May 22, 1954, 1184-1185.

The etiology of this condition remains obscure. Certain authors regard the lesion as the result of auto-digestion by activated pancreatic enzymes, resulting from acinar rupture taking place at the height of enzyme secretion. The fact that the lesion may occur in the wake of a recently ingested meal would tend to support this idea. Lium and Maddock (1948) reinforce this interpretation by animal experiments in which they produced pancreatic necrosis in starving rats by ligating the ducts and then stimulating the gland by artificial means. The most extensive inflammatory changes followed ligation of the ducts at the height of digestion, approximately 2 hours after the animal had eaten. Paxton and Payne (1948) stressed the role of alcoholism as an etiological agent. In two of the cases described there was a history of alcoholic tendencies.

The possibility of the lesion being primarily the result of vascular disease must also be considered. In two of the cases described ante-mortem thrombi were located in pancreatic arterioles not immediately related to necrotic tissue. This would tend to suggest that in the more acute forms of the disease there may well be a primary arteriolar thrombotic process giving rise to acute hemorrhagic infarction of the pancreas, with subsequent liberation and activation of gland enzymes. At any rate, the arteriolar lesions probably succeed in promoting extension of the lesion if not in initiating it, and may well be a main factor in rendering this type of pancreatic necrosis an irreversible and frequently fatal disease.

HEACOCK, C. H. AND CARA, D. J.: *Radiation therapy of pancreatitis*. Radiology, 62, 5, May 1954, 654-659.

Regardless of etiology, the authors have used x-ray therapy in acute pancreatitis in 53 cases in addition to the usual supportive measures. The results of such

treatment were regarded as good in 62 percent, fair in 29 percent and poor in 9.0 percent.

CHATTERJEE, P. K.: *Tuberculous peritonitis*. J. Indian Med. Assn., XXIII, 8, May 1954, 317-324.

After indicating the difficulties in the diagnosis of peritoneal tuberculosis, the author describes the treatment used in 52 cases. In the majority of cases, unless they are in advanced stages with extensive pulmonary disease, a course of specific treatment with streptomycin and P.A.S. for 4 to 6 weeks along with bed rest and general treatment followed by adequate after-care, and treatment of pulmonary or other lesions, is effective in arresting the disease. Although quite as good results are obtained with streptomycin, it is preferable to combine it with P.A.S. because, if treatment is prolonged, the chances of developing streptomycin sensitivity are great.

RADKE, R. A.: *Diagnosis and treatment of amebic liver abscess*. Ann. Int. Med., 40, 5 May 1954, 901-904.

From a study of 15 cases of amebic liver abscess, the following diagnostic criteria are established, (1) the presence of the clinical syndrome of amebiasis, (2) demonstration of intestinal lesions by sigmoidoscopic techniques, or demonstration of *E. histolytica* in aspirations or stools, (3) objective evidence of focal hepatic involvement, (4) unequivocal response to appropriate treatment.

Twelve of the cases had sharply localized pain in the liver with marked tenderness. The pain was always sharp and radiated to the back. In 6 cases the pain also radiated to the clavicle. Enlarged liver and weight loss were present in all cases. Elevation of the diaphragm was present in 10 cases, and an abdominal mass was palpable in three and demonstrated by x-ray and surgery in one additional case each. All were successfully treated with Atabrine and Carbarsone, surgical incision being required in 2 cases and thoracentesis in 2 cases. One death occurred from a complicating hepatic cancer.

OWEN, H. W., HOLMAN, C. B. AND PRIESTLY, J. T.: *Duplication of the stomach: report of a case*. Proc. Staff Meet. Mayo Clin., Apr. 21, 1954, 228-233.

Duplication of the stomach is very uncommon. Like duplications elsewhere in the gastro-intestinal tract, a pre-operative diagnosis is unusual. Duplications should be kept in mind as possible causes of acute abdominal symptoms. Best results are obtained by complete excision of the duplication, when possible. In the case reported herewith there was a small tube-like stomach just below the greater curvature of the first stomach with a separate opening into the duodenum. It was found by reflux of barium into the duplicate stomach during palpation at fluoroscopy. The case made a good recovery following extirpation of the duplicate.

GRIFFIN, J. P. AND GRIFFIN, C. G.: *Perforation of the stomach in a newborn due to a congenital defect*. J. Indiana State Med. Assn., 47, 6, June 1954, 619-621.

A case is reported, with autopsy findings of a perforation of the stomach in a newborn due to a con-

genital focal defect in the gastric musculature. In the acutely ill newborn child, an x-ray should always be made in the search for free air under the diaphragm. Diodrast should be used more frequently in an attempt to diagnose vomiting of obscure origin in the newborn.

Perforation of a peptic ulcer in the newborn is excessively rare, but more uncommon still is a perforation due to a rent in the wall of the stomach caused by a local defect in the musculature. Only 4 such cases appear in medical literature.

CHRISTENSEN, E.: *Meckel's diverticulum in an abdominal emergency*. Brit. Med. J., June 12, 1954, 1347-1350.

The complications of Meckel's diverticulum which call for emergency operation are infection, obstruction, intussusception, volvulus and hemorrhage. Cases describing each of these complications are presented. The diagnosis seldom is made correctly prior to operation. A true peptic ulcer may develop in a Meckel's diverticulum owing to the presence of aberrant gastric mucosa and hemorrhage and perforation may complicate such an ulcer. The most difficult cases surgically are those of ileo-ileal intussusception (or even ileocecal intussusception) in which resection of the gut sometimes is mandatory.

STEINBACH, H. L., CRANE, J. T. AND BRUYER, H. B.: *The roentgen demonstration of cirrhosis of the liver with fatty metamorphosis*. Radiology, 62, 6, June 1954, 858-861.

In a case of fibrocystic disease, an enlarged liver occurred. An x-ray film of the abdomen showed that the liver shadow was increased. Scattered throughout the liver were poorly defined areas of radiolucency. This was interpreted as indicative of cirrhosis with fatty change, and laparotomy confirmed the x-ray diagnosis. The child was about 4 years of age.

ORLOFF, T. L., SKLAROFF, D. M., COHN, E. M. AND GERSHON-COHEN, J.: *Intravenous cholangiography with a new contrast medium, "Cholografin"*. Radiology, 62, 6, June 1954, 868-870.

A new compound, introduced in Germany as "Bili-grafin," but now called "Cholographin" by its American Manufacturers (E. R. Squibb & Sons) is described. It reaches its maximum concentration in the main hepatic and common ducts in about 20 minutes, permitting diagnosis of calculi in the common duct in the post-cholecystectomy syndrome.

THEIS, F. V., SYLVESTER, J. AND SCHNELL, E.: *The problem of post-operative common duct stones*. Illinois Med. J., 105, 6, June 1954, 329-333.

The non-operative procedure for removing common duct stones, following operation, is not uniformly successful nor entirely safe. In the case reported by the authors, after persistent attempts to dissolve and expel the retained stones, surgery was required to effect their removal. In this case, in which ether was used as a flush, an elevated serum alkaline phosphatase

occurred and persisted for 5 months, although no other evidence of liver damage could be found. Recurrent cholecystitis has occurred following flushings.

POPPEL, M. H., ABRAMS, R. M., HANDELSMAN, J. AND SEGAL, A.: *Diaphragmatic herniation of the pancreas*. Radiology, 63, 1, July 1954, 91-93.

For the first time in recorded medical history, herniation of the pancreas through the diaphragm has been diagnosed by x-ray. This was rendered possible by the fact that the pancreas contained many calcareous deposits. The stomach and duodenum also were herniated due to increased abdominal pressure from an ovarian cyst. Surgery was successful in correcting all the conditions mentioned and a good recovery took place.

CANCELMO, J. J.: *Interstitial gastric emphysema, with report of a case*. Radiology, 63, 1, July 1954, 81-84.

The case of interstitial gastric emphysema reported was thought to be due to esophageal perforation. Only 4 other cases are reported in the literature and these all occurred following gastroscopy. In these cases the gas disappeared spontaneously. The condition must be differentiated from cystic pneumatosis (which usually affects the intestines) and from emphysematous gastritis, a serious highly fatal gastric inflammation due to gas-forming organisms. The chief roentgen finding in interstitial emphysema is a rather smooth line of radiolucency outlining the stomach wall.

FULTON, H. AND SANDWEISS, D. J.: *Intravenous cholangiography (Preliminary Report)*. Harper Hosp. Bull., 12, 3, May-June 1954, 106-111.

Cholografin, (E. R. Squibb and Sons, New York) is now available for visualization of the biliary tree and is of especial value in the search for duct stones, following cholecystectomy. Seventeen patients, who had their gallbladders removed, have been studied by this method at Harper Hospital with visualization of the common duct in all but one case. In four of the patients stones were demonstrated in the bile ducts.

JENKINSON, E. L., EPPERSON, K. D. AND PFISTERER, W. H.: *Primary lymphosarcoma of the stomach*. Am. J. Roentgen., Rad. Ther. and Nuc. Med., 72, 1, July 1954, 34-44.

Primary lymphosarcoma of the stomach, which is radiologically indistinguishable, as a rule, from cancer or even ulcer, is more common than previously believed. Eight cases are described in detail. When the x-ray findings are out of proportion to the patient's general condition, lymphosarcoma should be suspected. Life expectancy is somewhat greater than in carcinoma. One patient, with extensive involvement and perforation into the pancreas, is living and well 13 years after the lesion was demonstrated. Surgical excision and vigorous x-ray therapy offer much hope. Consequently it is urgent to explore all gastric malignancies regardless of how extensive the x-ray findings may be.

HISTORY OF ROSWELL PARK MEMORIAL INSTITUTE

In 1898 the New York State Legislature authorized the first appropriation of public funds ever made in this or any other country for combating cancer. The grant, for \$10,000, went to the Medical Department of the University of Buffalo for what was then called the New York State Pathological Laboratory.

The appropriation climaxed two years of effort by Doctor Roswell Park, Professor of Surgery at the University of Buffalo School of Medicine and a world renowned surgeon and scholar, and Mr. Edward H. Butler, Sr., Founder and Publisher of the Buffalo Evening News.

Both houses of the Legislature approved the request for the appropriation to support a cancer laboratory in 1897, but the proposal was vetoed by the Governor. Doctor Park, persisted, and the following year the proposal was favorably received by Governor Frank S. Black.

The first laboratory consisted of three small rooms at the University of Buffalo. Doctor Park was appointed Director and Doctor Harvey R. Gaylord, Associate and Pathologist.

This was the first laboratory of its kind in the United States with a staff who devoted all of their time to the study of the cancer problem. It was also the first laboratory in the world which devoted its efforts solely to the problem of cancer.

In his first annual report to the Legislature, submitted in January of 1899, Doctor Park warned that cancer "now is the only disease tabulated which shows a progressive and steady increase by weeks, months and years." The increase, he said, was "quite incompatible with the increase in population."

Doctor Park noted that tuberculosis "is perhaps the most widespread of all diseases and the most generally dreaded," and in 1887 was responsible for one out of every 499 deaths in the State, while cancer caused only one out of every 2,412 deaths. He warned, however, that "at the present rate at which this disease is increasing" it can be plainly seen that in the years ahead "cancer will be claim-

ing annually in New York State more victims than tuberculosis (consumption), smallpox and typhoid fever combined."

In 1901, gifts by Mrs. William H. Gratwick of North Tonawanda and others made possible the building of the Gratwick Laboratory, the first laboratory ever provided and equipped anywhere in the world especially for the study of cancer. Doctor Park felt that he was unable to accept the post of scientific director, and urged the appointment of Doctor Harvey R. Gaylord, who became the first permanent director of the Institute, a position he held until his death in 1923.

In the earliest years of the laboratory, research was directed into nuclear division, toxic substances as a factor in proliferation of malignant cells and epidemiological studies on "cancer houses" and districts. One doctor spent the spring and summer of 1902 at the laboratory studying sarcomas in rats, which he believed developed from an infectious agent picked up from the cages.

During studies made in 1904 and 1905, it was noted that immunity against cancer was evident in mice. These were the first such studies ever made. The possibility of a filterable virus, such as that of smallpox, being responsible for cancer was considered.

More than 250 compounds were also tested for possible chemotherapeutic activity by Dr. G. H. A. Clowes, the first screening program of its kind.

In 1910, Doctor Gaylord proposed the erection of a cancer hospital adjacent to the laboratory, the combination to be known as the State Institute for the Study of Malignant Diseases. He estimated that the "Institute" would require three dollars per year per case of cancer in New York State. That year the budget was \$27,000.

The following year, the Legislature passed a bill entitled "An Act to Amend the Public Health Law in Relationship to the Establishment of a State Institute for the Study of Malignant Diseases at Buffalo, Providing for Its Management and Control and Making an Appropriation Therefore." The law setting up the Institute outlined its function as follows:

"The Institute shall conduct investigations of the cause, mortality

rate, treatment, prevention and cure of cancer and allied diseases. Under regulations established by the State Commissioner of Health, there may be received free of charge in its hospital for study, experimental or other treatment, cases of cancer and allied diseases. The Commissioner of Health shall publish from time to time the result of its investigation for the benefit of humanity and he shall, from time to time collate its publications in a scientific report for distribution to scientific bodies and to medical scientists and qualified members of the medical profession."

On November 1, 1913, the new thirty bed hospital with provisions for a dispensary in the basement for an out-patient department was formally opened. During the same year, a state-wide pathological service was inaugurated. Through this service, all physicians of the State were able to submit tissues to the laboratory for free examination by competent pathologists.

At about the same time, a group of ten citizens purchased the thirty-one acre experimental farm at Springville and presented it to the trustees. A sum of \$15,000 was asked for the development of Springville. Also, \$100,000 was asked in order to purchase one gram of radium.

The first radium, 50 milligrams of it, was given to the Institute in 1914 by Mrs. Ansley Wilcox. This period also marked the beginning of the use of x-ray treatment for control of cancer. Before the outbreak of the European War, the use of radium and x-ray in the treatment of cancer was begun in Germany, France and England. The immediate result of the war was that research institutions in neutral countries, especially in the United States, began to carry out these new methods of treating cancer.

Experimental research during this period included attempts to discover chemical agents capable of exerting a selective destructive effect on cancer cells; the preparation of enzymes and chemical substances from tumors to determine if such substances were carcinogenic, and investigations of parasites.

In 1940, an additional hospital building was completed, bringing the bed capacity of the Institute to

108 beds. However, it soon became evident that these facilities would be inadequate to meet the demands made upon the Institute. With the enthusiastic support of Governor Dewey, plans were made for a marked expansion of hospital and research facilities.

When the present building program is completed, the Institute, with its extensive research laboratories and its 516 bed clinical unit, will be one of the largest cancer institutions in the world.

NOTICE

Albany.—Vastly expanded facilities for research into the causes, treatment, and cure of cancer are being made available in New York State with the opening of a new nine and one-half million dollar wing at the Roswell Park Memorial Institute in Buffalo.

Ceremonies marking the opening of the new wing were held in Buffalo October 14, with Governor Dewey and prominent figures in the field of cancer as speakers.

Subsequently, new laboratories for basic research in the fields of biochemistry and biology will be added in order to make the Institute a balanced investigative center. Plans for these projects are now on the drawing board and are expected to be completed in the near future.

With the new and enlarged facilities and an expanded staff of noted authorities in the field of cancer, the Institute will afford a unique opportunity for New York State to develop an integrated attack on the problem of cancer by bringing together basic research, clinical laboratory research, clinical investigation and patient treatment. In recruiting staff members, emphasis is being placed on obtaining clinicians who are not only proficient in their specialty but are also trained investigators.

The decision to center all aspects of the hospital program on cancer research actually is not a radical departure but a return to the basic principles under which the Institute was founded. The legislation establishing Roswell Park specifically provided that the Institute "shall conduct investigations of the cause, mortality rate, treatment, prevention and cure of cancer and allied diseases."

The proposed program at Roswell Park will be a research program in the sense that not only basic and fundamental research will be carried on, but also that every effort will be made to make the fullest research use of data accumulated from the treatment of patients.

The Institute will not be used as a terminal care facility, but for the active treatment and investigation of patients with all types of malignancies or with pre-malignant lesions. Similarly, the admission of patients with minor lesions which could be treated elsewhere will be discouraged, so that the Institute may better fulfill its purpose of contributing to the improvement of knowledge in the field of cancer diagnosis and treatment.

On the other hand, the Institute, through such facilities as two two-million volt X-ray machines and a linear accelerator, will be able to provide modalities of treatment not available in small communities. The surgical staff, too, will have the necessary adjuncts to perform radical complicated operations when they are indicated.

To be eligible for admission, a patient must be a resident of New York State and must be suspected of having or known to have a malignant or pre-malignant lesion. He must also be referred for treatment by a physician licensed in New York State.

Coincidentally with its expanded research and clinical program, the Institute will undertake additional educational responsibilities at the undergraduate, graduate and post-graduate levels, and is expected to develop into a graduate medical center for malignancy which will be second to none.

TROPHY

The Philadelphia Diabetic Society has just announced establishment of an annual trophy and cash award to promote independent medical research by doctors, medical students and research workers in the Philadelphia Area. The newly created Nathaniel N. Wolfsohn Award offers yearly prizes of \$500 and a gold plaque, and \$200 plus a silver plaque to authors of the best original papers on subjects related to the causes and treatment of diabetes mellitus.

An Award Committee of distin-

guished doctors from local hospitals and medical schools will select the prize winning papers. Presentation of the awards will be made during the annual May meeting of the Philadelphia Diabetic Society. Deadline for submission of papers in the current year's judging is April 1, 1955.

In announcing the Wolfsohn Award, Mrs. Gustav Ketterer, President of the Society, expressed the conviction of the Philadelphia Diabetic Society that, "citizen support of medical research is a vital and important adjunct to the progress of human civilization." Mrs. Ketterer pointed out that, "the purpose of this award is to promote and stimulate research in diabetes by medical scientists in the Philadelphia area."

"All papers submitted in competition for the Award must be original works on some phase of research in the field of diabetes," according to Mrs. Ketterer. "The Philadelphia Diabetic Society will make every effort to have winning papers published by a leading medical journal, with all copyrights and proceeds assigned to the authors on publication."

Mrs. Ketterer points out that, "since it is our aim as citizens to promote constructive medical research at home, anyone residing or working in the greater Philadelphia area is eligible to submit a paper in each yearly competition."

This year's Wolfsohn Award Committee judges include:

Charles L. Brown, M.D., Dean of Hahnemann Medical College.

Phyllis A. Bott, Ph.D., Professor of Physiological Chemistry, Woman's Medical College of Pennsylvania.

Abraham Cantarow, M.D., Professor and Head of the Department of Biochemistry, Jefferson Medical College.

Harrison F. Flippin, M.D., Associate Professor of Medicine, The Schools of Medicine, University of Pennsylvania.

F. D. W. Lukens, M.D., Director of Cox Research Institute, Professor of Medicine, University of Pennsylvania.

Harry Shay, M.D., Professor of Clinical Medicine and Director of the Samuel S. Fels Research Institute, Temple University School of Medicine.

Anthony Sindoni, Jr., M.D.,

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Chief of the Department of Metabolism, Philadelphia General and St. Joseph Hospitals.

The Philadelphia Diabetic Society was founded in 1938 to provide funds for the treatment and research study of diabetes. During its sixteen years of active service, the Society has given money to Women's Medical Hospital, St. Agnes' Hospital, Philadelphia General Hospital, Northern Liberties Hospital, Episcopal Hospital, Albert Einstein Hospital, Jefferson Hospital, Temple University Hospital and the Roxborough Memorial Hospital. In addition, the Society has provided funds to sponsor an educational program on nutrition and diabetes, in cooperation with the Medical Society Council.

Apparatus and equipment needed in the diabetic departments of these hospitals has thus been provided by this organization of interested, private citizens. The Society has also made funds available for camps for diabetics, drugs (including insulin) and milk for these camps, special therapeutic equipment, and in some cases money has been given to provide individual patients with necessary diabetic medication and treatment.

The Society membership is made up of citizens outstanding in civic work, and those interested in the welfare of diabetics. The only persons professionally connected with the Society are the members of an advisory board. This board is composed of a number of prominent physicians who treat diabetes and conditions immediately connected with or resultant from the disease.

The Society helps to make insulin available to all those who require it. Help is also given in providing artificial limbs, crutches and other appliances to those in need. Included in recent donations was a gift of 18 wheel chairs for diabetic patients at the Philadelphia General Hospital. At Christmas time each year, holiday cheer is brought to patients in the diabetic wards at Philadelphia General, through the efforts of the Society.

An educational program, sponsored by the Society, brings literature and lectures on latest trends in the treatment of diabetes to the general public. Emphasis is placed upon educating people to:

1. Recognize the early symptoms and signs of diabetes.

2. Realize the importance of early and adequate medical care.

3. Know the value of insulin, and discourage the fear of its use.

4. Beware of the danger of advertised nostrums.

Some of the research studies made possible by the contributions of the Society include: associated disorders (tissue, eyes, heart, limbs, etc.); the relationship of diabetes to premature hardening of the arteries; the relationship of this disease to kidney disorders (especially the fatal disease of uremia). A study of degenerative changes in the retina of the eyes and its treatment with testosterone was made possible through a Society grant. Funds provided jointly by the Philadelphia Diabetic Society and the National Heart Institute have made possible a study of the value of electrolyte therapy in advanced diabetic and non-diabetic renal disorders. Still another study supported by funds from the Society explored new avenues of approach to diabetic control—controlling the blood sugar level at the point where the patient has the greatest physical comfort, and at the same time consistent with his cardiovascular system and other possible existing complications. As a result of this exhaustive study, the new methods of compatible hyperglycemia control have evolved.

Sponsorship of the Nathaniel N. Wolfsohn Award is one of the Society's most ambitious undertakings. It is hoped that medical scientists in the Philadelphia area will be encouraged to undertake really significant research into the causes and treatment of diabetes mellitus.

INTERNATIONAL ACADEMY OF PROCTOLOGY AWARD TO ALBERT EINSTEIN COLLEGE OF MEDICINE

The International Academy of Proctology announces the establishment of a Teaching and Research Fellowship in proctology under the direction of Dr. Marcus D. Kogel, Dean of the newly formed Albert Einstein College of Medicine, New York City. The Academy has voted a \$1,000 Annual Grant for each of three years to assist in the development of research and educational projects in proctology at the University.

One of the suggested projects is

the establishment of a pathological tissue slide "library" for teaching purposes, under the direction of Dr. Alfred Angrist, Professor of Pathology.

The cornerstone of the Albert Einstein College of Medicine was laid June 13, 1954. The first class is scheduled to be admitted in September, 1955, with Dr. Marcus D. Kogel, former New York City Commissioner of Hospitals, as Dean.

EFFECT OF CITRUS FRUITS

A group of patients with chronic acne vulgaris showed "dramatic improvement shortly after the administration of vitamin C and citrus juices without change in the previous method of treatment," Dr. George E. Morris, assistant clinical professor of dermatology, Tufts College Medical School, reports. Writing in *Archives of Dermatology and Syphilology* (70:363 (Sept.) 1954), Dr. Morris describes a 4-month study involving 53 patients with acne vulgaris, all of whom were given an 8-oz. glass of citrus juice twice daily and ascorbic acid in dose of 3 gm. a day.

Forty-three of the 53 patients showed improvement, he states, but the most interesting were 15 whom he had observed for protracted periods prior to the study or who had been treated elsewhere without improvement. With these 15 patients, "the administration of vitamin C seemed to improve them more than any other mode of treatment that they had received."

Dr. Morris concludes: "This study seems to substantiate the findings of the British Medical Research Council in that vitamin C and citrus juices play an important part in certain cases of acne." The reference is to an experimental study of vitamin C deprivation.

PRESCRIPTIONS FOR AGED PERSONS ACCOUNT FOR THIRTY PER CENT OF PHARMACISTS DRUG VOLUME, SURVEY SHOWS

Prescriptions, refills, and over-the-counter sales for aged persons are now estimated to account for up to 30 per cent of the average pharmacist's drug volume according to a survey published in the July number of the magazine, *Pulse of Pharmacy*, published by Wyeth Laboratories.

Philip H. Van Itallie, editor of

the widely-read publication which is distributed quarterly to pharmacists throughout the nation, reported that druggists in cities, suburbs, and country towns were now filling more prescriptions for oldsters than at any previous time in their careers, and that the proportion was still growing.

The study was undertaken, according to Mr. Van Itallie, because prescription surveys do not give many clues to substantiate percentage breakdowns since antibiotics, antihistaminics, cough syrups, vitamins and many other drugs are

prescribed for the young and old alike.

A few druggists had actually captured the lion's share of the drugs prescribed by physicians for their patients in nearby nursing and convalescent homes. In one case a druggist secured \$12,000 worth of business annually from two nursing homes, both owned by one proprietor. In each instance it was learned that a reputation among local physicians for reliability and good service had been a major factor in the druggist's selection as the favored supplier.

CHOCOLATE-FLAVORED COMBINATION OF PENICILLIN AND THREE SULFAS ANNOUNCED BY PARKE, DAVIS & CO.

Detroit—Parke, Davis & Company has announced a new combination penicillin and sulfonamides product in palatable chocolate-flavored liquid form for physicians' use in treating infections.

The new product, called Penasoid Suspension With Triple Sulfas, combines crystalline potassium penicillin-G with sulfadiazine, sulfamerazine and sulfamethazine to combat infections caused by bacteria susceptible to these drugs.

"A combination of penicillin and sulfonamides often appears to be more effective against susceptible bacteria in lower dosage than either of these drugs alone," the company said, "and bacteria that are relatively resistant to either penicillin or sulfonamides are often sensitive to the combination."

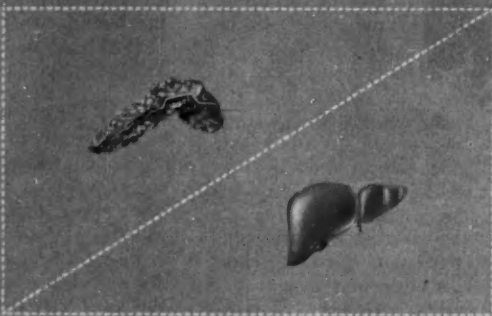
Each 5-cc. teaspoonful of the new combination drug contains 300,000 units of penicillin-G and 0.17 Gm. each of the three sulfa drugs.

The chocolate-flavored medicinal is indicated for treating patients with such conditions as lymphadenitis, otitis media, scarlet fever, tonsillitis, mastoiditis, erysipelas, gonorrhea, acute sinusitis, and urinary tract and certain other infections, the company said.

In addition, Parke-Davis pointed out, Penasoid Suspension With Triple Sulfas may be used to guard against secondary infection by susceptible organisms in patients undergoing tonsillectomy, tooth extraction, or other ear, nose and throat surgery.

The company said the dosage schedule of Penasoid Suspension With Triple Sulfas depends upon the patient's age, severity of infection and physician's judgment. However, they offered the following suggested dosages: Children under 1 year: 2 teaspoonfuls initially, then 1/2 teaspoonful every 6 to 8 hours; 1 to 5 years: 4 teaspoonfuls initially, then 2 teaspoonfuls every 6 to 8 hours; 6 to 12 years: 6 teaspoonfuls initially, then 2 teaspoonfuls every 6 to 8 hours; and adults: 6 to 8 teaspoonfuls initially, then 2 teaspoonfuls every 6 to 8 hours.

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TRADEMARK



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Penasoid Suspension With Triple Sulfas is supplied in 60-cc. bottles.

NEW PRODUCT FOR TREATMENT OF HYPERTENSION, CALLED SERFIN, ANNOUNCED BY PARKE, DAVIS & COMPANY

Detroit—A new product for the treatment of hypertension, called Serfin, was announced recently by Parke, Davis & Company.

Serfin is a pure crystalline alkaloid of *Rauwolfia serpentina* with

"the hypotensive action and tranquilizing effect of the whole root" of the shrub which is native to India, Ceylon, Burma, Cochin China, Malaya, Java and the Philippines, the firm said. *Rauwolfia serpentina* grows about three feet tall and has cylindrical stems, a pale bark and curved roots.

From early times, the roots, leaves and juice of *Rauwolfia* had been considered useful as an anthelmintic (remedy for destruction or elimination of intestinal worms), an antidote for bites of snakes and poison-

ous insects, and in the treatment of diarrhea, dysentery and cholera. Recently, interest in the shrub has grown as its hypotensive and tranquilizing action became better known.

"Because Serfin is a single alkaloid, uniform potency is assured and accurate dosage is attainable," the Parke-Davis announcement said.

The pure alkaloid is reserpine, and the company cited numerous clinical reports of its marked effectiveness in patients suffering from hypertension. Compared with other hypotensive agents, side reactions are generally mild.

RELIEVES MENTAL TENSIONS SO OFTEN PREVALENT

The average initial dosage of Serfin is one tablet three or four times daily for two or three weeks, the firm stated. If hypotensive response is adequate after this period, reduced dosage may be tried. Some patients may continue to show adequate response to a dosage reduced to two tablets daily.

"Serfin," Parke-Davis pointed out, "is useful in the treatment of the elderly arteriosclerotic patient in whom the use of hexamethonium and other potent hypotensive agents may not be advisable."

"The tranquilizing and sedative effects of the compound are also of value in the geriatric patient to relieve the mental tensions so often prevalent."

Hypertension is a symptom and not in itself a disease, so results and progress of therapy should be evaluated by considering the whole patient and not only his blood pressure reading, the company emphasized.

"While it is true that the easiest method to assess the effect of any hypotensive agent is to observe changes in blood pressure level after giving the agent, it is usually also true that taking the blood pressure unduly impresses the patient out of proportion to its importance. Although the so-called blood pressure 'expert' of the county fair and others can obtain a blood pressure reading with reasonable accuracy, it remains for the physician to interpret the value of the reading as it pertains to the patient."

Serfin is supplied as scored tablets, each containing 0.25 mg. reserpine, in bottles of 100 and 500, available on prescription only.

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| Niacinamide | 100 mg. |
| Pyridoxine Hydrochloride | 2 mg. |
| Calcium Pantothenate | 20 mg. |
| Ascorbic Acid | 300 mg. |
| Vitamin B ₁₂ Activity | 4 mcg. |
| Folic Acid | 1.5 mg. |
| Menadione (vitamin K analog) | 2 mg. |

Dosage: 2 capsules daily in severe pathologic conditions;
1 capsule daily when convalescence is established.

Supplied: bottles of 30 and 100.

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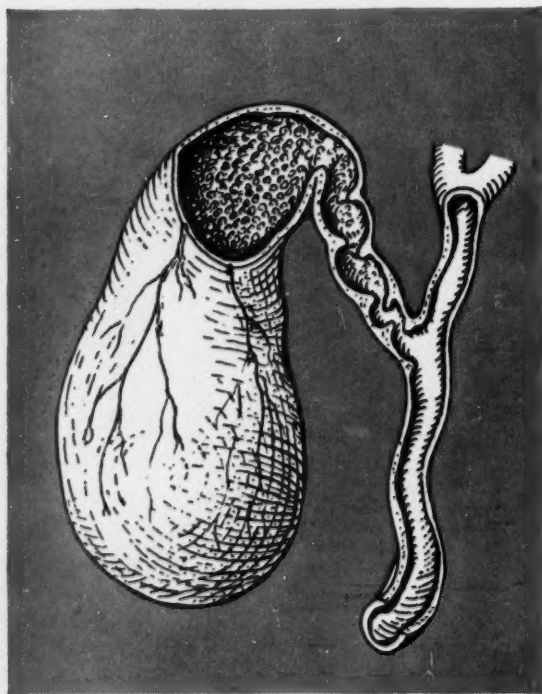
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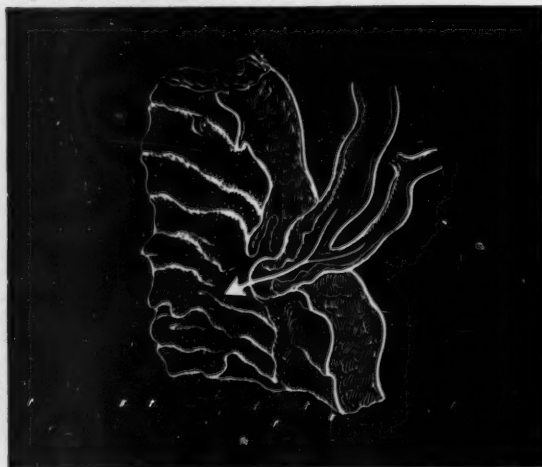
By increasing bile secretion with Ketochol® and controlling sphincter of Oddi spasticity with Pavatrine®, a free flow of bile is instituted with resultant symptomatic improvement.

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The average dose of Ketochol is one tablet three times daily with or following meals. The average dose of Pavatrine or Pavatrine with Phenobarbital is one or two tablets three or four times daily as needed. G. D. Searle & Co., Research in the Service of Medicine.

1. Berg, A. M., and Hamilton, J. E.: A Method to Improve Roentgen Diagnosis of Biliary Diseases with Bile Acids, *Surgery* 32:948 (Dec.) 1952.

Modern conception of liver cell.

